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The Cover Picture:
Mehmed Zaimović, a painting from the cycle, "Post Scriptum", tempera, 2005-2006, 50 x 76 cm.
Courtesy of Academy of Sciences and Arts of Bosnia and Herzegovina.

Qualitative analysis of the influence of concentric needle electrode components on motor unit potential

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In order to analyze the influence of Concentric needle electrode (CNE) components, 36 healthy volunteers were examined. MUAP parameters were analyzed after applying the manual method of extraction. The research was performed on the following muscles: m. vastus lateralis (MVL; depth of insertion were 0 cm/subfascial insertion and 1.5 centimetre (cm) perpendicularly (90^0) and obliquely (45^0) on muscle fibre direction, and temporal muscle (depth of insertion 0 cm/ subfascial insertion and 1.5 cm rectangular (90^0) on muscle fibre direction or parallel on fossa temporalis) on either side. In contrast to monopole montages, the qualitative EMG analysis confirmed that EMG potential detected with CNE is not relevant enough to determine the precise location of muscle (end-plate, tendon); compared with that of the central core waveform, the MUAP shape recorded by CNE is usually different. It has also been confirmed that cannula, albeit in rare cases, might have a "contributing" instead of "diminishing" influence on CNE MUAP parameters, and this, in turn, might lead to a wrong interpretation or even pathological findings. In view of the contributing effects of CNE components we recommend a qualitative division of MUAPs of healthy persons.

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Key words: Motor unit potentials, Concentric needle electrode.

Introduction

The muscular fibres of a single motor unit (MU) are distributed in the circular region of muscles stretching 5-7 mm in the upper extremities and 7-12 mm in the lower extremities (1). There is a somewhat higher density close to the centre of the region (2). The action potential of a motor unit (motor unit action potential MUAP, or motor unit potential MUP) reflects a summary of the activities of a certain number of muscle fibres of the MU during voluntary contraction. The first positive phase occurs when the impulse gets close to the recording electrode. The second negative phase occurs during depolarisation, while the third positive phase reflects repolarisation. The curve of detected

MUAPs in electromyographic (EMG) analysis consists of several components.

Amplitude is measured from the maximally positive to maximally negative deviation from MUAP. It is proportional to the number of activated musle fibres in the vicinity of the electrode. Lempe and Thile (1984) report the mean value of distance between the active muscle fibres and the electrode to be a more important factor than their respective diametre in regard to the MUAP amplitude (3). Potentially inactive fibres of other MUs can appear between those MU fibres which are dielectric and act as a filter, reducing the executive component of a single muscle fibre's potential (4, 5), exceeding 90% in only 200-500 μm (6).

Area: the surface of MUAP – reflects the values of duration and amplitude. There is evidence that 65% of MUAP area is built of 2 to 12 (on average 5) action potentials of muscle fibres (7).

Duration: denotes "deviation from", and "return to" the base line. It is also defined as the initial and final point of the slow component of MUAP. The greater the variations between the speed of conducting of the MU fibres, the longer the duration of MUAP. It is a reflection of the temporal and spatial summation of the electrical activities of MU muscle fibres (8). It is also the most reliable indicator of a pathological process (9, 10).

Number of phases: " number of crossings of the base line of MUAP plus one". MUAPs commonly have up to 4 phases, while those with 5 or more phases are the so-called polyphasic potentials. This depends on the synchronisation level between muscle fibre potentials in the vicinity of the electrode (11).

Turn implies a revision of polarity which does not cross the base line during the phase. When MUAP consists of more than 5 turns it is called "serrated" or "complex".

In neuromuscular diseases the MUAP configuration is disturbed. In neuropathological diseases the collateral reinnervation after the release of particular motor units increases the size of MU, resulting in the increase of the amplitude and duration of MUAP. The incidence of polyphasic MUAPs can increase. The most reliable criterion for *miopathy* is a shorter duration (11) along with a complete recruiting sample of lower amplitude, accompanied by the increase in the number of polyphasic MUAPs.

However, in MUAP analysis it is necessary to know the features of the recording electrodes. In order to record the biological electric activity it is necessary to have two electrodes. When both electrodes are placed close to the source of electric activity the mode of recording is determined to be bifocal or bipolar, but if one electrode is placed at a distance from the source, we have a monofocal or referential recording. Regardless of this, a certain amount of electrical activity of the tissue is recorded from both electrodes. In practical performance the *concentric (coaxial) needle electrode (CNE)* is composed of the central core which serves as the „active" electrode and of the outer part, cannula serving as a referential electrode. But the cannula itself is not entirely indifferent (12); its potential equals the mean value of tissue potential along the surface of the electrode (13). In a routine EMG analysis MUP is, in fact, the difference of potentials recorded either by the central core or cannula.

The aim of this research was to confirm modes in which MUAP parameters, recorded by CNE, change in healthy persons, dependent on the activities of its components (the central core and the cannula).

Subjects and Methods

The research was conducted on 36 healthy volunteers of both sexes (21 or 58 % males), and average age of 33±11 years. The research was performed on the following muscles: m. vastus lateralis (MVL) and temporal muscle on either side. Depth of insertion were 0

centimeter (cm) or subfascial insertion, and 1.5 cm perpendicularly (90°), parallel (0°), and obliquely (45°) on muscle fibre direction for MVL, and 0 cm/subfascial insertion, and 1.5 cm rectangular (90°) to muscle fibre direction and parallel on the temporal fossa for temporal muscle. Subfascial insertions were detected by "insertional activity" and used as starting points for deeper (1.5 cm) insertions. The data collection of the MUPs was obtained manually – by applying the method of "averaging". The total number of MUPs collected for MVL was 52 for subfascial insertions and 50 for deeper (1.5 cm) insertions. The total number of MUPs collected for temporal muscle was 42 for subfascial insertions, and 40 for deeper insertions. Only characteristic MUPs, regardless of their incidence rate, depth of insertion, or kind of muscle were selected for analysis. As is well known, the MUP analysis itself is qualitative by nature, implying only quantitative MUP recordings without taking into account their incidence rate.

Simultaneously, on three separate channels we presented the potentials recorded between the diminishing surfaces of CNE, and separately, of the CNE recordings between the cannula and central core with the distant surface referential electrode placed on the skin above the patellae. MUPs were recorded during a looser, voluntary contraction while calculation of their average value was performed until the elimination of "artefacts". Respecting the criteria established by Stålberg et al. (1986) only MUPs were selected and analyzed with amplitudes over 50 μV (9) and a rise time of the initial positive to negative slope of less than 0.5 ms.

Medelec - Synergy EMNG apparatus was used in the present analysis. The filters were positioned at frequencies between 20 and 20.000 Hz. The MUP analysis was carried out with the enlargement of 20 μV/cm.

Results

The typical examples of triphasal MUPs obtained manually by the method of „averaging" – are presented in Figure 1. Activities of such MUPs are recorded by the central core. However, qualitative analysis showed a significant deviation of the MUP morphology from the „classical" triphasal ones. The highest activity of such MUPs is recorded by the central core. On the other hand, quantitative analysis showed significant deviations of MUP morphology from the „classical" triphasal ones. Although these features divide potentials roughly into several groups, each particular group may contain elements from the other groups apart from the dominant ones. The following MUP groups were detected:

I MUP which reflects realistically or fictionally the end-plate (EP) or tendon (figure 2 and 3);

II MUP with the amplitude recorded by CNE being higher than that recorded by the central core (figure 4)

- A. The central core is in the territory of MU, while the cannula contributes to the CNE amplitude.
- B. The central core is far from the MU, while the cannula, positioned in the territory of MU, contributes significantly to MUP

III MUP wherein both the cannula and the central core register different fibre populations (figure 5)

- A. The CNE potential is indented, while that of the central core is smooth, and vice versa
- B. A greater number of phases in the central core from MUP to CNE

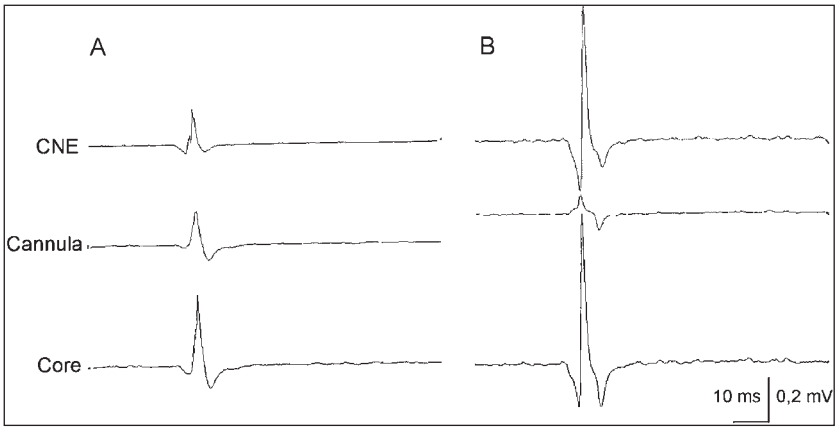

Figure 1 Examples of MUP obtained manually – by method of averaging
– From top to bottom: potential recorded with CNE by a cannula and central core MVL, insertion 90^0, depth1.5 cm.

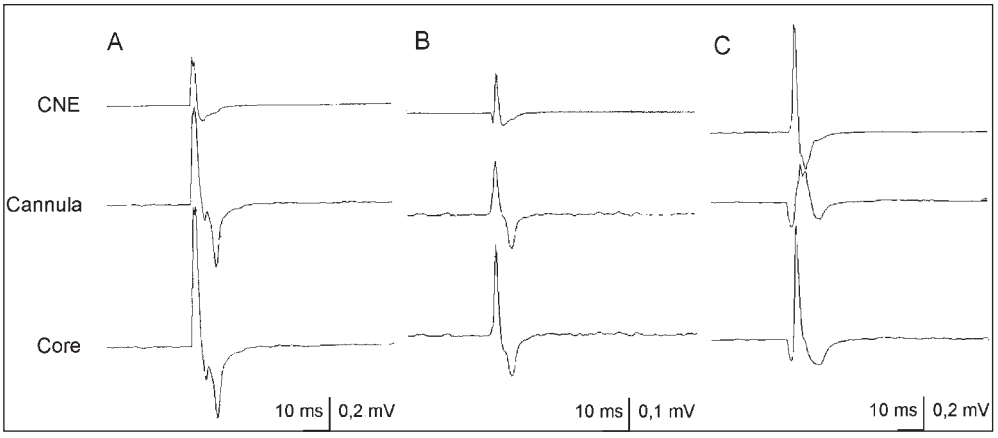

Figure 2 MUPs which reflect really or fictitiously end-plate (EP)
A. Region of EP. Classical example of bipolarl (-+) waveform on all channels. MVL, subfascial insertion. B. Region of EP, but diminishing of the cannula (channel 2) from central core (channel 3) gives 3 phases on CNE. MVL, subfascial insertion. C. Impression of EP on CNE because of diminishing of the cannula (channell 2) from central core (channel 3). MVL, insertion 45°, depth1.5 cm.

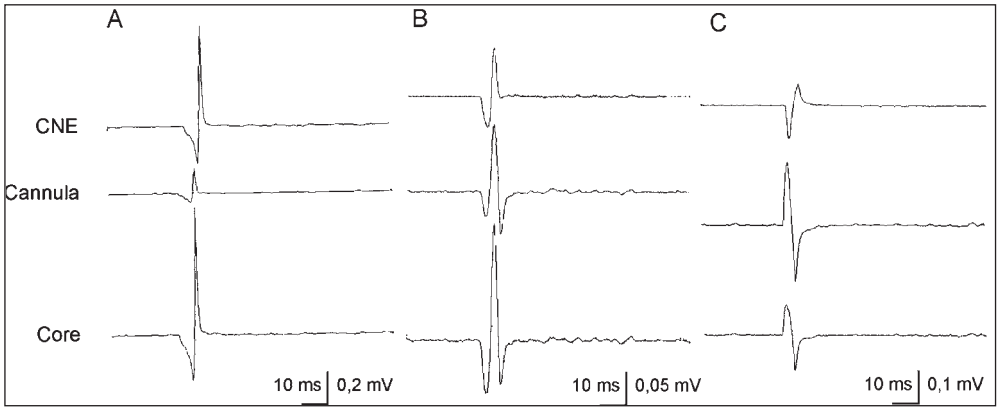

Figure 3 MUPs which reflect the tendon really or falsely
A. Region of tendon. Classical example of bipolar (+-) waveform on all channels. MVL, insertion 90°, depth1.5 cm. B. Impression of tendon on CNE because of diminishing of cannula's final positivity (channel 2) from central core (channel 3); shorter duration. MVL, insertion 90°, depth1.5 cm. C. Dominant contribution of cannula whose MUP (channel 2) is bigger than MUP of central core (channel 3). Region of EP (visible on channels 2 and 3), but diminishing of cannula from central core provides a false tendon shape on CNE with +-phase. Temporal muscle, insertion 90°, depth 1.5 cm.

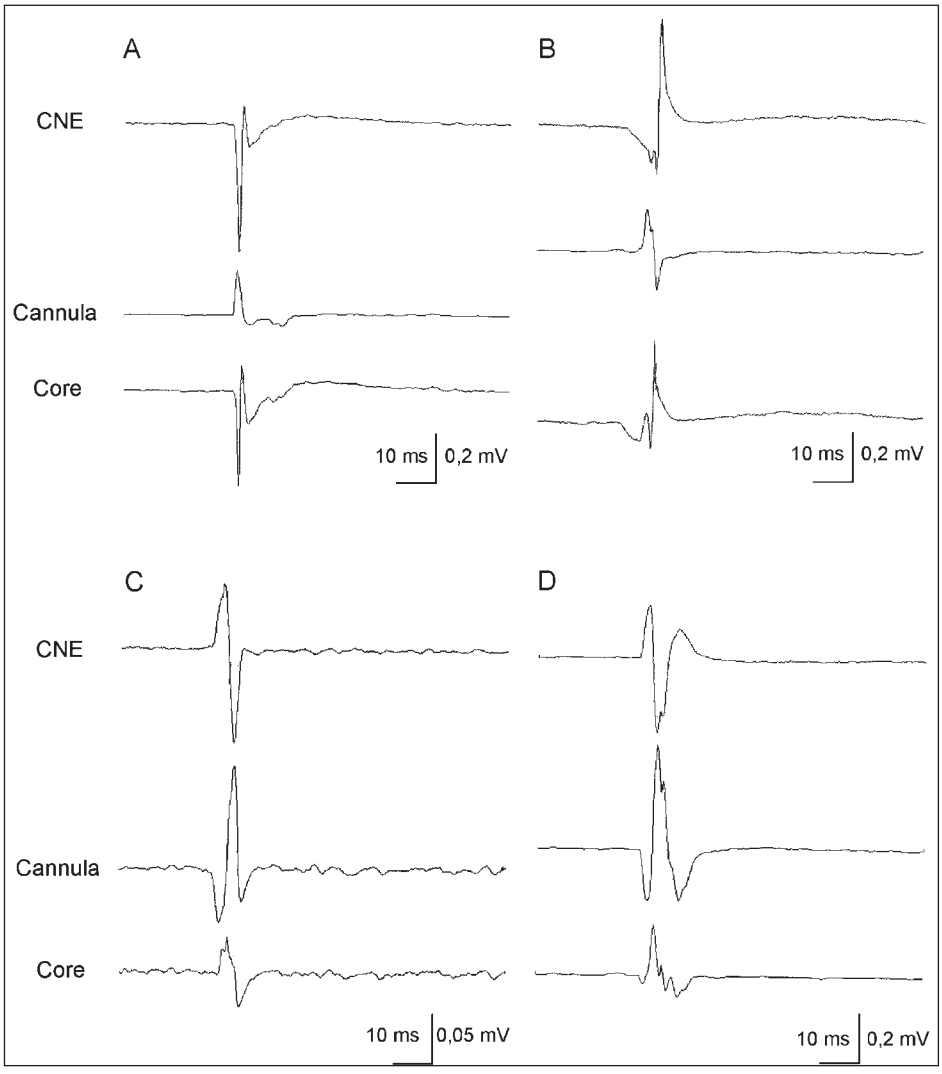

Figure 4 MUP whose amplitude recorded with CNE is larger than that recorded with central core
A, B. Central core is in MU territory with a cannula contributing to CNE amplitude. MVL, insertion 90°, depth1.5 cm. C, D. Central core is located far from MU while the cannula, located in MU's territory, contributes dominantly to MUP. MVL, insertion 90°, depth1.5 cm.

Discussion

The first MUP group consists of MUPs which really or falsely reflect the end-plate (group IA, figure 2) or tendon (group IB, figure 3). The typical MUP lacks the initial positive component after CNE insertion in the EP region (figure 2A) and as a result, the bipolar (-+) MUP remains on all channels (cannula 2, central core 3). However, after insertion into the EP region, it is possible to record three phases with CNE due to the differing arrival times of the main negative peak of MUP on the cannula or central core and of the „diminishing" of the cannula from the central core (figure 2B). A false impression of end-plate on the CNE because of the „diminishing" of the initial positive component along the cannula from the central core is also a possibility (figure 2C).

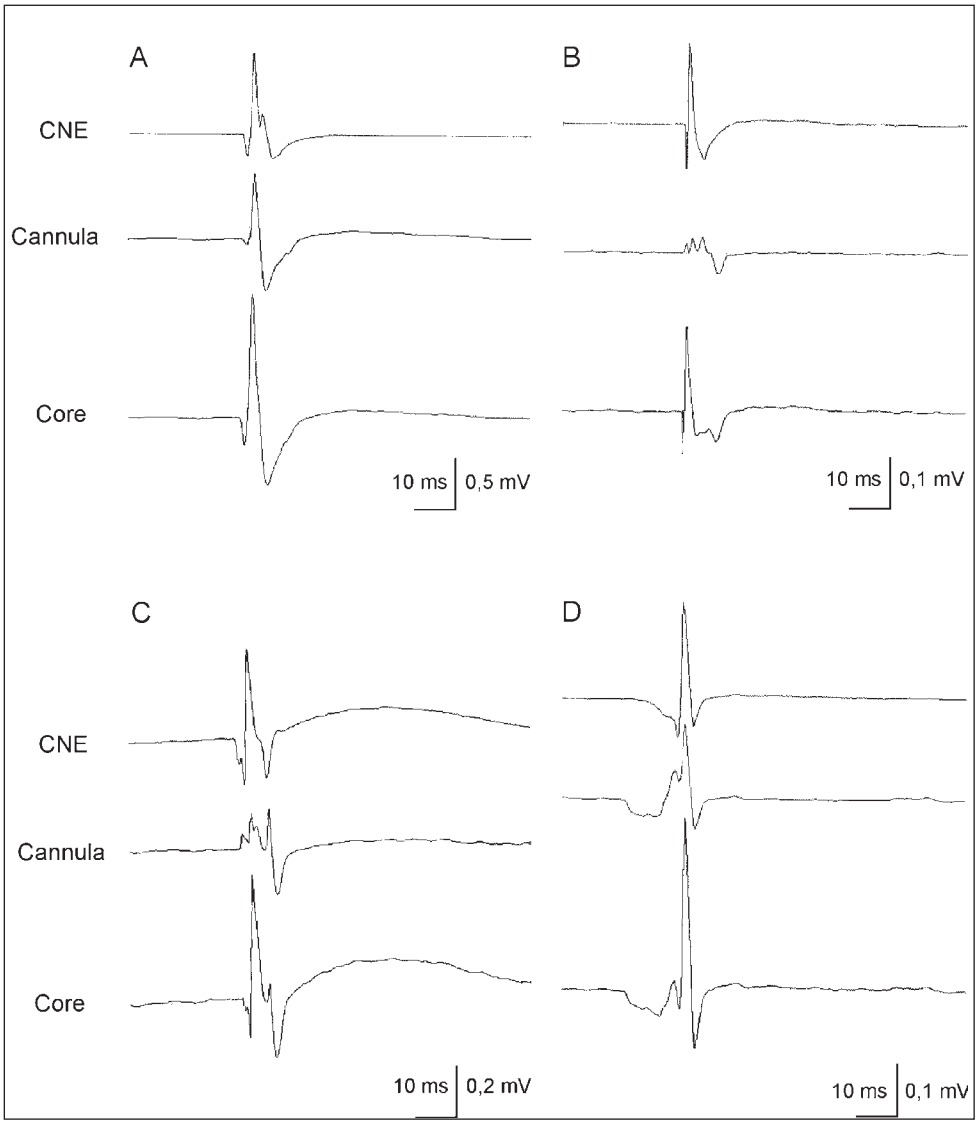

Figure 5 MUPs wherein the cannula and central core detect various fibre populations. Potential of CNE is serrated while that of the core is smooth, and vice versa, A. Various fibre populations are detected by the cannula (channel 2) and central cores (channel 3). The result is a serrated but triphasal potential of CNE (channel 1). MVL, subfascial insertion. B. Central core (channel 3) and cannula (channel 2) detect their own fibre population. Fractions of cannula (like macro- EMG). MVL, subfascial insertion. C. A bigger number of phases on central core from MUP on CNE. Central cores (channel 3) and cannula (channel 2) register different fractions. Polyphase of potential registered by central core (channel 3), but diminishing of fractions provides CNE's potential (channel 1) which has three phases. MVL, insertion 90°, depth1.5 cm. C. One fraction of MU is detected in the same manner by both electrodes (cannula on Channel 2, and central cores on channel 3), and that is being diminished on CNE (channel 1), and as a result (instead of several phases or serrations smooth potential emerges on CNE). MVL, subfascial insertion.

A classical example of a bipolar (+-) waveform upon the CNE insertion in the region of the tendon is recorded on all channels (figure 3A). However, there is a possibility of a false „impression" of the tendon on the CNE because of the „diminishing"

final positivity of MUP which is gathered thanks to the cannula from the central core MUP (channel 3) so that the CNE MUP is of a shorter duration (figure 3B).

The finding in figure 3C is very interesting. In this case the CNE is inserted in the region of the end-plate (which is visible on channels 2 and 3 where initial positivity of the MUP is missing), but the „diminishing" of the cannula MUP from the central core MUP gives a shape of the tendon on the CNE with a +- phase. Here, it is obvious that the contribution of the cannula is significant to MUP of a higher amplitude in relation to MUP of the central core, positioned farther from the MU than the cannula (and as such, it has a smaller MUP amplitude),. The cannula's negativity provides the initial positivity for the CNE while its positivity provides the final negativity for the CNE. Taking into consideration the fact that such potentials shorten the duration of MUP on the CNE, it is possible to obtain not only a false picture of the location but also to come to a false judgment of a myopathic process in certain circumstances.

The following MUP group (group II) displays an amplitude recorded with CNE higher than that recorded by the central core (figure 4).The figure 4A displays the MUP with the obvious difference of the observed fractions of the core located in the MU territory (a higher amplitude) in relation to the cannula. Negativity of MUP on the cannula within the MP, lacking the initial positivity, appears at the similar time as the initial positivity of the MUP onto the central core, and consequently, thanks to this „addition" contributes to an increase in amplitude of the MUP's initial positive phase on the CNE. The negativity of the MUP collected from the central core remains relatively unchanged in relation to the CNE. The final result is that the CNE has a higher MUP amplitude than the central core (group II A). In the case of the „contributing" influence of the cannula, the pattern on CNE might be falsely diagnosed as neuropathic.

Similar findings were recorded in the next example (figure 4B). The cannula MUP contributes to the MUP amplitude on the CNE so that the potential is of a higher amplitude than that on the central core whose MUP is still of a higher amplitude in relation to cannula, and thus it is „closer" to the MU's territory. Here, the first negative phase of the MUP recorded by the central core is annulled.

In both examples the central core is located in the MU's territory while the cannula contributes to the amplitude of the concentric needle electrode potential (group IIA).

The MUPs follow recorded with the central core located far from the motor unit (group IIB) while the cannula, located in the motor unit's territory, contributes by and large to the motor unit's potential (figure 4C and 4D). Figure 4C displays the bipolar (-+) MUP recorded with CNE which, in fact, reflects the region of the end-plate. The peak of the central core is far from the MU so that the MUP, collected there, is of an amplitude lower than that of the cannula, but at the same time is bipolar (-+). The classical triphasal MUP of the cannula prevails since it is closer to the MU's territory, and this is obvious from its higher amplitude in relation to central core's MUP. Because of the initial positivity of the cannula which is "added" to the initial negativity of the central core the first-negative phase occurs on the CNE of a higher amplitude than the negative phase of the MUP on the central core. On account of the main negative phase of the cannula MUP the final positive phase on the CNE occurs. Here erasure occurs of the identical, final positive phases of MUPs of both the central core and cannula. The CNE displays MP of the end-plate with two fractions (-+). Regarding MUP in the IIB group there is a larger number of phases of motor unit potentials of the central core than of the CNE.

In the next example (figure 4D) it is obvious that the peak of the central core is located far from the centre of the MU's territory, and as a result, MUP of a lower amplitude has been recorded. The MUP of the cannula prevails because it is located within the territory of the MU. On account of the initial positivity of the cannula MUP the first-negative phase on the CNE MUP occurs. In this example there is no erasure of the final positive phase of the central core (being smaller) and the cannula (being larger), resulting in the final, negative deviation on the CNE. As a result the CNE displays three unusual fractions (-+-).

There follow MUPs (group III) wherein the cannula and the central core register different fibre populations (figure 5)

In the IIIA group the potential of the concentric needle electrode is indented while that of the central core is smooth, and vice versa (figure 5A). The MUP of different fibre populations detected by the cannula and central core is displayed. The result of the "diminishing" of the main negativity of the cannula MUP in relation to that of the central core is an indented, but nevertheless, triphasal (+-+) MUP on the CNE.

Also, in the next example (figure 5B), the central core and cannula register different fibre populations. At this, fractions of the cannula MUP have the same shape as those in the macro EMG. The final positivity of the central core is indented, but thanks to the „diminishing" of fractions of the cannula MUP there follows a relatively smooth final positivity of MUP recorded with CNE.

In the next example (figure 5C) the central core and cannula also register different fractions of MU. In this case we can observe the polyphasal MUP registered by the central core. „Diminishing" of fractions results in MUP with three phases on the CNE.

In the next example (figure 5D) both electrodes (the cannula and the central core) register one fraction (initial positivity) of MU in the same mode which, in turn, is „diminished", resulting in a smooth, shorter MUP recorded with CNE instead of several phases or indentations.

A larger number of phases or turns in CNE bipolar montages is sometimes a result of the „greater influence" of individual components (cannula, central core), which does not necessarily reflect temporal dispersion since, for example, the classical and „smooth" triphasal MUPs in the central core and cannula arriving at different times may yield, due to „diminishing", four or more phases of MUP recorded with CNE. Nevertheless, qualitative analysis has also shown the reverse possibility – sometimes the effect of temporal dispersion and poliphasy in the central core and cannula is erased, and as a result, MUP recorded with CNE has fewer phases.

Dumitru et al. (14) report the initially negative deflexion for the two illustrative MUPs recorded with a central core-cannula montage. Deflexion occurs because of the potential recorded by the cannula in the cannula-surface montage which is greater in relation to the potential recorded by the central core. By so-called "differential amplification" a comparatively greater initial positive deflexion recorded by the cannula is transformed, and consequently, that negativity is „diminished" with the initially positive deflexion of the central core, resulting in the residual negative potential which is the onset of MUP (12). We have also observed similar phenomena of „diminishing" in our study.

In the case of the cannula recording a relatively higher potential in relation to that of the central core, especially in relation to the initial and final segments of MUP, it is understandable that the central core-cannula potential will display the same duration as the central core-surface electrode potential. By contrast, if the cannula and central core detect a similar onset and end of MUP, the final duration of MUP will depend on the dominant signal in any temporal location

with the possibility of constructing MUP of a shorter duration for the central core-cannula montage (12, 13, 14).

Conclusion

The qualitative analysis has confirmed that it is not possible to determine the precise location of muscle (end-plate, tendon) on the basis of EMG findings with CNE as is the case with monopolar montages, but also that the shape of the CNE MUP is usually different from that of the central core. At the same time, it has been confirmed that cannula can occasionally have a „contributing" rather than a „diminishing" influence on CNE MUP parameters (amplitude, duration, number of phases) which, under certain circumstances, may lead to the wrong interpretation of EMG findings.

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From *virtual library* over *dictum* and *intel* until *refine*: a story about ten-years of reform of medical education in Bosnia-Herzegovina

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The purpose of this paper is to recall how we, medical teachers in Bosnia-Herzegovina (BH), coped with the challenge of reform in higher education and to analyze what in our doing was fashion, which trends we have chosen to follow, and what were the real, substantial and tangible results of our work. Financial support for reform across the board came through the Trans-European Program for Co-operation in Higher Education in Central and Eastern Europe (Tempus), and, since 1997, the five schools of medicine in Bosnia and Herzegovina partnered with academic institutions from nine EU countries in seven granted Tempus projects. The results were tangible: a network of medical libraries was established; medical schools were assessed internally and externally; several important documents were drafted and agreed on; a core group of faculty from Bosnia and Herzegovina was trained in new teaching methods; and research was done and published. Not less important, there were also some less tangible, but perhaps even more important fruits of this cooperation. A sense of trust was established, which is essential for any future collaborative action. Representatives from all sides, previously divided by the war, had a chance to communicate with each other, dispelling some prejudices and regaining belief that it is possible to work together. This example of the schools of medicine of Bosnia and Herzegovina shows that higher education can be a favorable arena for reconciliation. Financial incentive can serve as a catalyst in the process and the presence of impartial partners (in our case, schools of medicine from the EU) proved beneficial for establishing and maintaining trust and good-will. The conclusion is that society rebuilding can be promoted indirectly, through formal education and professional engagement, not necessarily by pressing the "opposing" sides to talk about reconciliation and sign peace declarations.

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Key words: Medical education, Tempus, ECTS, Quality assurance, Curriculum reform, Catalogue, Knowledge and skills.

Introduction

Since the end of the past millennium, all over Europe the Academia has been in a state of high anxiety and high fever. The name of the new virus, which is widespread, is well known: the Bologna Process. The recommended cure appears to be a simple one: a substantial reform of higher education. For those who understand the Process seriously, over the Academia is hanging, like the Damocles sword, a threat of the year 2010 – at that time you will be reformed or you will perish. As a natural consequence, the past decade has seen concerted attempts to reform (or revolutionize) undergraduate medical training. There is no general consensus; advocates for change are still claiming that traditional teaching is old-fashioned and too detailed and produces doctors with skills not sufficient for our world today (1, 2).

The purpose of this paper is to recall how we, medical teachers in Bosnia-Herzegovina (BH), have coped with this challenge and to analyze what in our actions was fashion, which trends we have chosen to follow, and what are the real, substantial and tangible results of our work.

Curriculum

Apparently, in every higher institution a reform starts and ends with curriculum change. There are many definitions of a curriculum, and we will try to simplify the terminology issues. *The curriculum* is a word originally derived from the Latin: *currere* mean to run, and *curriculum* is literally a race course, referring to the course of deeds and experiences through which children grow and mature in becoming adults. In Academia[1] of today the definition of curriculum is more complex and by curriculum we understand the set of courses and their content, linked together and gradually leading to a degree in science or arts. Therefore, the curriculum could be observed as a main frame on which the educational institutions are built and which represents the expression of educational ideas in practice. Once the curriculum's main frame is defined, we are able to design the detailed course of study or *syllabus***.** Certainly the curriculum is not written down and engraved in stone; just the opposite, its peculiar feature is a permanent demand for fine tuning and changes. The majority of schools have an Office of Medical Education and a Committee for Curriculum Reform in permanent session. The curriculum must be responsive to changing values and expectations in education if it is to remain useful.

This is not the end but the beginning of the story: the curriculum devised by academic experts should be readily transformed into practice by the administration and finally experienced by students (or customers, as some in this age of corporate culture prefer to address them). Three quite different curricula have been identified: (i) the planned curriculum, (ii) the delivered curriculum and (iii) the one actually experienced by students (1). It would be far beyond the scope of this paper to discuss all of them or even some more: we will stick with the story about how we initiated the reform of the medical education process, how we designed a new curriculum for all Bosnia-Herzegovina (BH) medical faculties, and ending with the current process of designing a new curriculum for the Faculties of nursing studies.

Was a curriculum reform in Bosnia and Herzegovina (BH) a luxury or necessity?

Many in academic and non-academic circles would argue that in post-war, politically undefined, unstable, and economically de-

[1] Gr. academeia, olive grove sacred to Athene, six stadia outside of Athens, in which Plato assembled his students and started teaching. This olive grove belonged to Academos and was accordingly named Academia.

stroyed Bosnia and Herzegovina (BH), there were more important goals to reach, tasks to accomplish, and priorities to follow than the reform of medical education (4, 5). Our reasoning was simple: no society has a future without high-quality education capable of producing fully trained experts in all disciplines. Therefore, society will have to adhere to contemporary trends and developments in education (6). We believed that there was a mutual consensus on all levels in BH that education is the key to any development strategy. Finally, to be honest, each of the universities was exposed to pressures, both internal and external.

Internal pressure for reforms

The authorities of all Medical Schools expressed unanimously their willingness to raise the standards of medical education and to establish a new culture of teaching, comparable with that in more developed countries. There were many reasons for this decision and we will discuss some of them.

Pride and self-esteem

It is immanent to human nature to strive to be a part of an institution (movement, project, or enterprise) that is accepted and recognized on a larger scale. It was reasonable to expect that all participants in our project would enthusiastically join efforts with the common goal: to bring the performance of their institution as close as possible to existing European standards.

Fundamental changes in the essence of medicine

Secondly, all participants in the educational process are aware that medicine today is rather different from that just a decade or two ago. The same is true for the teaching environment, methodologies, strategies, and tools. Beside, the hopes, dreams, and motives that attract students to study medicine are different. The most obvious difference is the molecular revolution – not an exotic issue anymore, reserved only for the prophets with a vision and especially gifted. We witness that scientific discoveries are embedded more and more deeply into the routine of everyday medical practice. New technologies reach across the borders of different disciplines, and extend the power of human senses and skills far into the universe of the human body.

As one thing leads to another, medicine practiced in the developed world has almost doubled the human life span in less than a hundred years, significantly increasing the importance of chronic and old age's diseases. These medical areas should be incorporated in every future curriculum. Thus, when defining the curriculum content, educational priorities should be to teach medical students about the chronic status of an ailing old body rather than a detailed account of some exotic diseases.

Managed care

Not least important, we are witnessing the domination of "*managed care*," which is nothing but a euphemism for exclusively profit-oriented medicine. Corporate medical practice, the market economy, and consumer culture are transforming health care (7). There is an unquestionable demand on physicians to rely exclusively on disease management protocols to improve outcomes, reduce costs, and standardize care (8). Personalized care tailored to individual needs of patients becomes a thing of the past. From the Academia standpoint, these changes have dramatically influenced the physician-patient relationship and the moral mission of health care. How should we prepare students to cope with the unbearable increase of hospital costs, be productive under the demand of contemporary hospital management, and still be caring, compassionate, and dedicated physicians?

External pressure for reforms

Pressure from the community

The pressure of the non-academic world on Academia is growing and rightfully so. Society wants a simple answer to a simple question: is health care (certainly based on good medical education) good enough given the funds invested? The physicians are not unquestioned majesties anymore. The public today demands physicians who respect them, who are able and willing to communicate clearly, and who honor their wishes about health care (8).

Influence of the social environment

The political structures, with the main and single wish to please the public with the pretext of care for the "common good", are prone to blame physicians for all evils in the health care structure and increasingly demand "*accountability*" of health care professionals.

Pressure from the "Customers"

Students and their parents ("clients/customers") want to know if the curriculum of an institution is up-to-date and comparable to its counterparts around the world. A very simple, yet very important, question is being increasingly asked: "*Is the certificate of graduation received at the end of a long period of hard work and many sacrifices good enough to secure a career worldwide*"(9)?

Bologna process

Beside this growing "hidden" informal pressure, it will not take much longer for formal pressure to become strong. Over the last ten years, the process that started as informal discussions has becomes "a must." All over Europe there is little question if everybody will accept the Bologna principles and recommendations (10, 11), in part or as a whole; the single remaining question is how quick will we be in the adaptation process. Only those who choose to remain on the *pariahs* side of the world will question this growing dogma – and we do not know many of them (10-13).

Accreditation process pending

Frankly speaking, in BH – but not only in BH – there are too many Medical Schools with respect to the size of the population and to the financial resources of the country. It is to be expected that a rational country leadership will support the very best among them and withdraw support from institutions unable to play well on the international scene. The Schools that will be able to pass through an accreditation process in the near future will be accepted in respectable company. The principal features of an institution capable of producing the type of physician that society needs and which are scrutinized during any accreditation process are (a) competency to offer the curricula in accordance to European standards, (b) recognition on the basis of its achievements worldwide, (c) eligible partners in European student mobility schemes, (d) fully integrated into the credit transfer system, and (e) linked to the global network (14, 15).

Fashion

Last, not to be neglected, there is the eternal issue of fashion. We define fashion in medical education as an approach to education that is based primarily on social (or political) influences, in contrast to approaches based on established educational principles and theories, critically evaluated experiences, or the results of valid research. An analogy is the distinction between fashion in clothes (color and style) and the quality and functionality of clothing (material and comfort). Maybe multi-professional learning and multimedia computer aided learning are case studies to illustrate why each should currently be characterized as a fashion rather than informed

practice. Both have received international attention in medical curriculum reform (16).

Reform of medical education: what and how we did it?

First step: Development of medical libraries

Mostar Medical School was established in 1997. The priority of the school officials was then to define the curriculum, organize the admittance exam for the first generation of students and elect the teaching faculty for the first year of study. From the very beginning we were aware that an institution without a library cannot exist as an academic institution, and we focused all our efforts on establishing one. Due to the fact that the recent war in BH caused enormous damage to both human and material resources, a library system was non-existent when we started with the project. Mostar was among the cities whose libraries were completely destroyed. In 1998, we submitted a project proposal to the European Commission Tempus program. The project was approved and granted 166,000 €, and the contract was signed in February 1999. In April 1999 we started the implementation of the project. Despite the fact that the project was aimed at the development of a library at Mostar School of Medicine, we decided to invite all medical schools in BH to participate.

Assembling the five University Schools of Medicine in BH in the early post-war period to work together on curriculum reform was a mission close to impossible. The wounds had not been healed and prejudices and suspicions were strong. Still, the academics from the Schools of Medicine exhibited a fair amount of common sense and unanimously decided to join the projects. Strong support was offered from our EU partners, Andalusia School of Public Health, Granada, Spain; Help the Children Fund, Cork, Ireland); Medical Faculty University of Heidelberg, Germany; Universita degli Studi di Firenze, Italy; Ghent University School of Medicine, Belgium and Semmelweis Medical University, Budapest, Hungary.

We jointly developed the project's concept and objectives, being aware that we had to lean on global information networks and to aim to become a part of the international librarian's "visible colleges," in order to provide users (our teaching staff, students but medical personnel, too) with full and easy access to information, combined with the possibility of interlibrary loans and the acquisition of photocopies at reasonable costs. The main principles of our concept were that;

– traditional, 19th century style libraries with huge collections of books and journals are fast becoming relics;

– a library's purpose is not only to house the collection but to provide access to all information needed;

– the library of the 21st century is to become a virtual one, it's "collection" and information is not held on shelves but worldwide.

Following the above mentioned principles, we organized the first BH inter-library network. In addition to the initial funds, we received considerable support in information technology equipment, software, books and journals, total worth exceeding one million euros. The full list of achievements was published elsewhere (17-19).

Next step: curriculum reform

Working together on the library project, we understood that all BH Medical Schools, from the biggest and oldest to the smallest and newest one, were faced with many, commonly shared difficulties. Although each School proudly claimed that it offered "*excellent and state-of-the-art education to students, equal to European standards*", we could not tell whether this was true: the indicators and evidence to support such claims were

missing. On the other hand, there was some evidence that medical education in our region could not be considered to be of high quality. Not a single school in the region ever reached the Times list of 500 best medical schools, our graduation certificates are not readily accepted worldwide, the number of international students in BH was lower than 30 or 40 years before, and our students and teaching staff were not included in the European mobility scheme. Thus, the reality was not as bright as we would have liked it to be. Blaming the war and post-war times for all our problems, misconducts, and failures was not a good excuse anymore and obviously, reforms were badly needed.

Quality of medical education in Bosnia and Herzegovina or how good are we really?

As a starting point, it has been important to find an answer to this question from the very beginning. In 1999, the Mostar University School of Medicine participated in a self-evaluation exercise within the Association of European Universities (CRE)/Phare-sponsored project "Institutional Quality Assurance" (20). Feedbacks received on the report that followed from this self-evaluation were an useful starting point (21, 22) and strengthened our belief that we needed a substantial curriculum reform.

Internal and external assessment

Financial support for curriculum reform across the board came through the Trans-European Program for Co-operation in Higher Education in Central and Eastern Europe (Tempus). At the start of our work, the first task was an attempt to systematically analyze the situation in which BH medical schools work. There were no hard evidences to support the claims we encountered during the initial discussions with the faculty managements, who more or less unanimously stated (and probably firmly believed) "our medical school is as good and on the same level as European ones, in some aspects maybe even better!"

As an initial experience, an *ad* hoc analysis of the Strength, Weaknesses, Opportunities, and Threats (SWOT), Table 1, revealing the overall status of BH Schools of Medicine helped us gain a better insight into "how good we were" (23).

This work offered a general overview, but in order to support it with hard facts we decided to perform an in-depth self-assessment, followed by an external assessment in each of the schools. Those assessments were done by European experts with respectable credentials. This certainly was not only one of the first such studies in BH but also one of the first such all national-level quality assessments worldwide.

During internal assessment, schools consistently either overrated their overall functioning (Foča/East Sarajevo, Mostar and Tuzla) or markedly overrated or underrated their performance on individual items on the survey (Banja Luka and Sarajevo). Scores for internal assessment differed from those for external assessment. These differences were not consistent, except for the sections 'School mission and objectives', 'Curriculum' and 'Development plans', which were consistently overrated in the internal assessments. External assessments were more positive than internal assessments on 'Students' and 'Facilities and technology' in 3 of the 5 schools. This assessment exercise in 5 medical schools showed that constructive and structured evaluation of medical education is possible, even in complex and unfavorable conditions (24).

This exercise proved (despite many difficulties, egos hurt and ensuing arguments) that medical schools in Bosnia and Herzegovina have successfully formed a national consortium for formal collaboration in curriculum development and reform.

Table 1 Analysis of strengths, weaknesses, opportunities, and threats (SWOT) of Medical Schools in Bosnia and Herzegovina

Features assessed by SWOT analysis	Banja Luka	Mostar	East Sarajevo	Sarajevo	Tuzla
Strengths					
Teaching in blocks of knowledge	no	yes	no	no	no
Rational use of laboratories	no	yes	no	no	no
Up-to-date library	no	yes	yes	no	no
Permanent survey of students' opinion	no	yes	no	no	no
Extensive use of Internet resources	no	yes	yes	no	no
International projects	no	yes	no	no	yes
Students' exchange program	no	yes	no	no	yes
Good permanent v. visiting staff ratio	yes	no	no	yes	yes
Weaknesses					
Visiting professor dominant	no	yes	yes	no	no
Poor interest of young MDs for basic science	yes	yes	yes	yes	yes
Poorly developed research infrastructure	yes	yes	yes	yes	yes
Lack of space & equipment	no	yes	yes	no	no
Slow Internet connections	yes	yes	yes	yes	yes
Insufficient integration in teaching	yes	yes	yes	yes	yes
Insufficient institutional support	yes	yes	yes	yes	yes
Opportunities					
Awareness of the Bologna Process	yes	yes	yes	yes	yes
Faculty supportive of reforms	yes	yes	yes	yes	yes
New grants from the European Union	yes	yes	yes	yes	yes
Well-established cooperation on the national level	yes	yes	yes	yes	yes
Strong support from European schools	yes	yes	yes	yes	yes
Threats					
Overall political environment	yes	yes	yes	yes	yes
Lack of institutional support	yes	yes	yes	yes	yes
Meager financial resources	yes	yes	yes	yes	yes
Legal background confusing or missing	yes	yes	yes	yes	yes
Loss of enthusiasm	yes	yes	yes	yes	yes

Outputs

Strategic documents

With the assessment we established a firm ground and starting point, as well as the missing yardstick – from this point on we were able to measure and properly judge our achievements. The next step was to define the aims, objectives and outcomes to be achieved. Thanks to the external assessment, we had a clear insight into our strengths and weaknesses, which considerably facilitated our definition of goals. On this foundation ten working groups (WG) were formed, to develop a number of documents, regulations, recommendations and catalogues. Each of these groups consisted of a working

group leader (exclusively responsible for final output), other full members were the experts from each of five BH medical schools, assisted by an expert from an EU country. The organizational scheme and participating universities are presented in Table 2.

Each of the working group performed in a satisfactory manner, and as tangible outputs, after three years work and many discussions, we have as results of these joint efforts:

1. New curriculum for medical education, based mainly on Heidelberg University new reformed curriculum, with integrated European Credit Transfer Points (25)
2. Mission statement (26)
3. Proposal of admission criteria, students transfer criteria and rules for students' mobility (27)
4. Graduate profile and expected list of competencies (28)
5. A review article on application of contemporary information technologies in medical teaching and learning was published (29) and a platform for distance learning was established in Aarhus University, Denmark (30)
6. Students assessment & graduation criteria (31)
7. Students transfer criteria (32)
8. Manual for organization of quality assurance (33)
9. Manual for application of new teaching methodologies was published (34)
10. Catalogue of knowledge and clinical skills published (35)

Faculty training

Training in quality management

Two seminars were held in Heidelberg, one on quality management in higher education with 14 participants and another on new teaching methodologies, with 25 participants from BH, Croatia, Slovenia and Hungary. Quality management training was continued through another Tempus project, granted in 2005 (Quality Management in Medicine, *Qumamed*, CM SCM-C005A05-2005), coordinated by East Sarajevo University, and Katholieke Hogeschool Sint-Lieven, Belgium as contractor (36).

Training teaching and assessment skills

On the basis and results of the Dictum project we proposed as logical continuation, the Integrated Teaching and Learning in Medicine (*Intel-M*), which was granted and started in September 2005 (CD-JEP-19037-

Table 2 Organizational scheme of the Working Groups

Working Group	University in charge	EU support university
WH for new curriculum	Mostar	Heidelberg
WG for mission statement	East Sarajevo	Vienna
WG for admission criteria	East Sarajevo	Gent
WH for students transfer	Sarajevo	Vienna
WG for assessment and graduation	Tuzla	Heidelberg
WG for profile of competencies	Sarajevo	Gent
WG for new teaching and learning methodologies	Mostar	Heidelberg
WG for catalogue of knowledge and clinical skills	Mostar	Aarhus
WG for quality assurance	Mostar	Heidelberg
WG for application of information technologies in teaching	Banja Luka	Aarhus

2004). The project was coordinated by the East Sarajevo University Medical Faculty and the Heidelberg University, Germany has had the responsibility of the project's contractor. During the three years of the project's lifespan (it will end in October 2008) activities have been focused on the introduction of new teaching methods with emphasis on the training of clinical skills early in the undergraduate medical education, as well as on new approaches to student assessment.

At the beginning of the *Intel –M* each of the five BH medical faculties selected three to five teachers for one-week intensive training at the Medical Faculty Heidelberg and they become "core groups" which started to implement the new teaching methods. After several follow up training courses most of these highly enthusiastic young teachers were capable of performing to full capacity as trainers of trainees for their colleagues. Two training sessions were held in BH in Jahorina and Neum, granting the dissemination of new knowledge and sustainability of results. An important side effect was the intensive exchange of teachers between all the BH Medical Faculties and an increase in communication at a personal level. Core groups organized the seminars at Medical Faculties outside of BH, at Split University, Croatia and Belgrade University, Serbia. A booklet introducing new teaching and assessment was published by Sarajevo University Medical Faculty (37) and in cooperation with teachers from the Heidelberg Medical Faculty, the Project Consortium is working on an online manual, where the different new methods would be described.

Implementation of ECTS

This one year project, aimed at introducing the ECTS system to BH medical faculties, was granted in 2006 (CM-SMC-CD10A06-2006) and ended in January 2008. The project was coordinated by the East Sarajevo University medical faculty. This project facilitates the official implementation of ECTS at all Medical Faculties; moreover an online template for the easy handling of the ECTS at the faculties was installed on a local server in Foča, BH, as an open access source. This was an instrument to serve all faculties as a comparative basis for ECTS implementation. An important side effect of this project was its influence on the quality of the content and formal reorganization of the undergraduate courses, because the teaching objectives had to be significantly improved in relation to student work loads, the newness of the presented knowledge and final outcomes. All these activities influenced the quality of medical education, in spite of the project's short life of only one year.

Students mobility

Over the past ten years we have been able to organize clinical training for students in Heidelberg, Germany and in Cork, Ireland. Many institutions and organizations have supported these activities: Heidelberg and Cork University; Help the Children Fund and Surgeon Noonan Society from Ireland (http://www.ucc.ie/students/socs/noonan/about.shtml), Rotary Club from Speyer, Germany (www.rotary.de/speyer). On average, each year from 1998 until today, 10-20 students have been placed in hospitals (from two to four weeks), to be trained in surgical and internal medicine clinical skills.

Research and publications

In the early phases of collaboration of the BH Medical Schools we were both satisfied and proud of our accomplishments and results. Still, our work was invisible to the larger academic community. The dissemination of our results was poor and communication with the international scientific community close to zero. Fortunately, these problems were solved in 2003, when the staff of the

Croatian Medical Journal (CMJ), led by its editors-in-chief, Professors Ana and Matko Marušić, offered professional support and assistance in presentation and publishing our results. Intensive publishing activity started early in 2004, when the CMJ editors invited us to publish an editorial on curriculum reform (23) and invited us to join the International Campaign for Revitalization of Academic Medicine (ICRAM) (38, 39). Encouraged by these early achievements, we decided to start research work on curriculum reform, and the results exceeded all our expectations. We performed internal and external quality assessment in all five Medical Schools in BH, which was one of the first national-level assessments of this kind worldwide (24). In the years to follow, we performed a survey on students' attitudes and knowledge about science (40) and staff's attitudes on the curriculum reform (41). Treatises on medical education and reconstruction of the health sector in Bosnia and Herzegovina were published (42-44), as well as students' research (45-48) and international clinical research (49).

Probably the most demanding task was the creation of the "Catalogue of Knowledge and Clinical Skills" which was another demanding enterprise, and took more than one year. Thirteen medical schools (Vienna, Austria; Gent, Belgium; Aarhus, Denmark; Heidelberg, Germany; Split and Zagreb, Croatia; Chieti, Italy; Ljubljana, Slovenia and 5 schools from BH) from 8 European countries joined in these efforts. There were 16 co-editors and 120 experts, who covered all fields of clinical medicine. The Catalogue was published by "Medicinska naklada" in the CMJ Book Collection (35).

Conclusion

Since 1997, the five schools of medicine in Bosnia and Herzegovina (Banja Luka, East Sarajevo, Mostar, Sarajevo and Tuzla) partnered with academic institutions from EU countries in seven granted Tempus projects. The first project "Virtual Medical Library Development" (3-5) granted in 1997, was followed in 2003 by the "Development of an Integrated Medical Curriculum" (*Dictum*) in 2003. Five more TEMPUS projects were approved and granted, in which medical schools from BH partnered with 17 universities from ten European countries (Vienna, *Austria*; Gent and Leuven, *Belgium*; Osijek, Split and Zagreb, *Croatia*; Aarhus, *Denmark*; Heidelberg, *Germany*; Budapest, *Hungary*; Chieti and Florence, *Italy*, Cork and Dublin, *Ireland*; Ljubljanja and Maribor, *Slovenia* and Granada**,** *Spain*).

The results were tangible: a network of medical libraries was established; medical schools were assessed internally and externally; a number of important documents were drafted and agreed on; a core faculty group from Bosnia and Herzegovina was trained in new teaching methods; new teaching and learning equipment was purchased and installed and research was done and published. During the last four years over 20 journal articles have been published, some in the leading biomedical journal, such as The British Medical Journal, Brain and The Lancet, e.g. and The Lancet.

Currently we are working on a three-year project "Reform of education in nursing, *Refine*," whose principal objective is to design a new curriculum in nursing at the university level, in three cycles in accordance with the requirements of the Bologna Process standards. Beside the new curriculum, we hope we will be able to produce all other substantial documents needed for comprehensive reform, including the "Catalogue of Nursing Skills" – the work is in progress.

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Finally, we believe it appropriate to conclude this overview by expressing our deep gratitude for the financial support provided through the Trans-European Program for Cooperation in Higher Education in Central and Eastern Europe (*Tempus*). Thanks to this support the substantial progress in reform of medical teaching in all BH medical schools and faculties for nursing studies was possible.

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Determinants of milk and milk product consumption among primary school children in a district of Ankara, Turkey

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Aim. Determination of influencing factors of milk and milk product consumption among a group of primary school children in Ankara. **Methods.** In this cross-sectional study, the study population consisted of 356 students in two grades (5th and 8th), and 335 (193 5th grades, and 142 8th grades). The participation rate was 94%. The SPSS program 15.0 was used for data entry and basic statistical analysis. The chi-square test for cross tabulations and logistic regression to identify influencing factors of milk consumption were used. **Results.** Of the 335 students; 193 were in 5th grade, and 142 were in 8th grade. The mean age was 10.1±0.4 in 5th grade, and it was 13.3±0.7 in 8th grade. In the logistic regression analysis significantly positive associations were determined between "milk consumption of the students" and the grade (OR=6,934, 95%CI=2,634-18,254; p<0.001), male sex (OR=2,713, 95%CI=1,220-6,030; p=0.014), presence of milk at home everyday (OR=2,935, 95%CI=1,086-5,281; p=0.030), buy milk with pocket money (OR=2,303, 95%CI=1,036-5,121; p=0.041), eat breakfast everyday (OR=4,994, 95%CI=2,161-11,541; p<0.001), and prefer to drink milk instead of cola (OR=2,961, 95%CI=1,210-7,248; p<0.001). **Conclusion.** School-based interventions to promote milk consumption in earlier grades with a holistic approach can contribute to children's understanding of the health benefits of milk at earlier ages.

Key words: Children, School, Milk, Consumption.

Introduction

There has been strong evidence of an association between consumption of milk throughout life and health status. The contents of milk, such as immunoglobulin, growth hormone, enzyme inhibitors, antibacterial agents, protein and peptides, fatty acids, vitamins, minerals are essential for life (1). Because milk and other dairy products have beneficial effects on bone health, obesity, serum total cholesterol (TC), blood pressure, chronic diseases including some types of cancer (2-6), recommended dietary intake

guidelines have been developed for different age groups, sex, and specific conditions such as pregnancy 700 g (baby), 400 g (child), 350 g (adolescent), 250 g (adult), 350 g (elderly), and 500 g (pregnant woman) (7).

Infancy and childhood periods are given specific importance because human beings learn most of their behaviors at younger ages. Learning to drink milk at these ages is made necessary by a number of factors such as inadequate nutrition education, existence of negative role models (parents, etc), having different soft drink options, the physical and biological properties of consumed milk (heat, type, etc) (8, 9). Economical factors are additional limitations for milk consumption in the Turkish community. Such factors determine the different consumption prevalence in different countries.

Milk consumption was predominantly localized to countries in Europe, however, there has been a shift recently to Asian countries (10). In 2002, the annual per-capita consumption of fluid milk in Turkey was found to be 20 kg, and this amount is behind other developed countries (11).

Studies to define the milk consumption amount and to determine the related factors may contribute to the solution of increasing the consumption amount in childhood. With this perspective, this study was conducted to investigate possible influencing factors such as socio-demographic characteristics, regular breakfast consumption, and the pocket money spending preferences of primary school pupils in Ankara.

Methods

Subjects

The study schools were the two schools in the Primary Health Care Unit region where the researchers had to work for their internship period (two months). The participants consisted of 335 students (193 5th graders, and 142 8th graders). The total population was 356 students and the participation frequency equal to 94.1%. Six students were not at school, and 15 students were busy with some other social activities during the study.

Two different grades (5th and 8th grades) were assessed. The main reason for having two different grades was to define the age influence on milk consumption. The mean age was 10.1±0.4 in the 5th grade, and it was 13.3±0.7 in the 8th grade.

Instruments

Assessment of milk intake

Final year medical students with one academic consultant assessed food intake by means of a brief self-administered diet history questionnaire. The questionnaire asked about the frequency and amount of ingestion of selected foods including milk, yogurt, and other milk products. One cup of milk or 1 dish of yogurt was generally considered 1 serving in Turkey.

According to the number of servings of milk consumed, participants were classified into five groups: no intake, 1-2 per month, 1-2 per week, 3-6 per week, every day.

Procedure

Prior to the study, a pre-trial of the questionnaire was conducted in a socio-demographically similar school on 20 students. The questionnaire was re-formed due to the feedbacks before the study.

Data Analysis

The SPSS program 15.0 was used for data entry and basic statistical analysis. The dependent variable of the study was *"everyday milk consumption";* and there were various independent variables. The chi-square test was used to compare frequencies between the independent variables and "milk consumption of the students". A $p < 0.05$ was

considered significant. Odds ratios (OR) and 95% CI were calculated in the logistic modeling to identify influencing factors on milk consumption (grade, sex, think that milk prevents diseases, presence of milk at home everyday, buy milk with pocket money, eat breakfast everyday, prefer to drink milk instead of cola).

Results

Of the 5th grade participants, 104 were male (53.9%) and 89 female (46.1%). Of the 8th graders, 73 were male (51.4%) and 69 female (48.6%). Fifth and eight grade students were similar in terms of sex ($p = 0.660$), number of siblings ($p = 0.605$), family type ($p = 0.871$), number of households ($p = 0.674$), and receiving pocket money status (0.06) (Table 1). As expected, the two groups were statistically significantly different by grade ($p < 0.001$). The mean age was 10.1 ± 0.4 in 5th grade, and it was 13.3 ± 0.7 in 8th grade (Table 1).

Milk consumption increased by age. The students in 5th grade consumed milk less than the 8th graders ($p < 0.001$). The frequency of everyday milk consumption among the 8th graders was higher compared to the frequency in 5th graders ($p < 0.001$). The amount of consumed milk did not statistically significantly differ between the two grades ($p = 0.140$) (Table 2).

In the logistic regression analysis; *"everyday milk consumption of the students"* had significantly positive associations with grade (OR = 6.934. 95%CI = 2.634-18.254; $p < 0.001$), male sex (OR = 2,713, 95%CI = 1,220-6,030; $p = 0.014$), presence of milk at home everyday (OR = 2.935. 95%CI = 1.086-5.281; $p = 0.030$), buy milk with pocket money (OR = 2.303. 95%CI = 1.036-5.121; $p = 0.041$), eat breakfast everyday (OR = 4.994. 95%CI = 2.161-11.541; $p < 0.001$), and prefer to drink milk instead of cola (OR = 2.961. 95%CI = 1.210-7.248; $p < 0.001$) (Table 3).

Discussion

Milk is a major contributor of protein and calcium as well as other food elements to the body. Milk intake changes due to age, gender, and specific conditions such as pregnancy. For children it is probably equal to 400 gram (two-three cups) per day (12, 13). In our study population, both the milk consumption frequency and milk intake (grams of milk) decreased by grade (Table 2, 3). This might have been caused by a number of factors. First, the probability of being exposed to environmental stimulators in terms of soft drink consumption could have increased with age. And there is evidence that higher consumption of soft drinks was inversely related with consumption of milk in young children (9, 14). Second, the response of the students to such exposures may be different at different ages and the parents' influence might have been weakened as age increases.

Gender influence was found to be a predictor of less milk consumption in some studies. For example, calcium intake by the females related with inadequate milk consumption was determined among Asian children (15-17). In our study, gender was also found to be a determinant for milk consumption. The frequency among males was statistically significantly higher compared to the frequency in females (OR = 2.713; 95%CI = 1.220-6.030; $p = 0.014$) (Table 3).

The economic status of the family is associated with healthy food intake in general and the presence of milk every day at home might be closely dependent on the purchasing power of the family. In a study from China conducted in 2002 showed that the frequency of milk drinking among 12-14 year old adolescents was strongly associated with high socio-economic status (18). Although we did not have detailed information in terms of the families' economic status, we found a strong relationship between milk consumption and the presence of milk

Table 1 Socio-demographic characteristics of the students (October, 2007)

Characteristics	5th grade		8th grade		p
	Number	%	Number	%	
Sex					0.660
Male	104	53.9	73	51.4	
Female	89	46.1	69	48.6	
Age					
Mean±SD	10.1±0.4		13.3±0.7		
Median	10		13		
Number of siblings					0.605
<2	89	46.1	59	41.5	
2	68	35.2	51	35.9	
>2	36	18.7	32	22.5	
Mean±SD	1.76±1.13		1.95±1.38		
Median	2		2		
Nuclear family					0.871
Yes	167	86.5	124	87.3	
No	26	13.5	18	12.7	
Number of households					0.674
<4	84	43.5	65	45.8	
4	63	32.6	40	28.2	
>4	46	23.8	37	26.1	
Mean±SD	3.91±1.23		3.92±1.42		
Median	4		4		
Receive pocket money					0.065
Yes	147	76.2	95	66.9	
No	46	23.8	47	33.1	
Total	193	100.0	142	100.0	

Table 2 Milk consumption status (October, 2007)

	5th grade		8th grade		p
	Number	%	Number	%	
Milk consumption					
Yes	187	96.9	107	75.4	<0.001
No	6	3.1	35	24.6	
Everyday milk consumption					
Yes	144	74.6	47	33.1	<0.001
No	53	25.4	95	66.9	
Amount consumed per day (cup)					
≤2	121	54.8	100	45.2	0.140
>2	72	63.2	42	36.8	
Mean±SD	2.43±1.67		1.50±0.78		
Total	193	100.0	142	100.0	

Table 3 Predictors of "everyday milk consumption" of the students (October, 2007) (n = 335) [a]

	Milk consumption status [b] n(%)	Adjusted OR (95% CI)	p
Grade			<0.001
5th*	75.4	1.0 [c]	
8th	96.9	6.934 (2.634-18.254)	
Sex			0.014
Female	83.5	1.0 [c]	
Male	91.5	2.713 (1.220-6.030)	
Think that milk prevents diseases			0.451
No	83.4	1.0 [c]	
Yes	91.9	1.356 (0.614-2.995)	
Presence of milk at home everyday			0.030
No	82.6	1.0 [c]	
Yes	90.5	2.935 (1.086-5.281)	
Buy milk with pocket money			0.041
No	79.6	1.0 [c]	
Yes	90.9	2.303 (1.036-5.121)	
Eat breakfast everyday			
No	59.1	1.0 [c]	<0.001
Yes	92.1	4.994 (2.161-11.541)	
Prefer to drink milk instead of cola			
No	81.3	1.0 [c]	<0.001
Yes	94.5	2.961 (1.210-7.248)	

[a] Logistic regression model included grade, sex, presence of milk at home everyday, buy milk with pocket money, eat breakfast everyday, prefer to drink milk instead of coke. For each category, other variables were adjusted.
[b] Percentage without adjustment
[c] Reference category

at home every day (OR = 2.935, 95%CI = 1.086-5.281; p = 0.030) and buying milk with pocket money (OR = 2.303, 95%CI = 1.036-5.121; p = 0.041) (Table 3).

In this study we had a number of limitations. First, we conducted this survey in 2 primary schools. For this reason we cannot generalize the results. Second, milk consumption and other information were determined from the personal statements of the students with a "food and milk consumption" survey. An observation based method is a more objective way to get more "objective" data which we recommend for further studies.

School-based intervention can contribute to children's understanding of the health benefits of milk. Children will choose healthier options from canteens such as milk. The key to success in this regard is to ensure student involvement (19). After the study, we planned and organized conferences at the study school. We conducted the conferences for the schools and grades differently. The teachers were also invited to the conferences. In the last 10 minutes of the conferences, the questions of the students were answered by the presenters.

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Evidence-based medicine and clinical practice

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Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence in making decision about the care of individual patients. The practice of evidence-based medicine integrates physician's individual clinical expertise, best available research evidence, and patient unique values in the process of decision-making about the health-care. It should be accompanied by evidence-based patient choice. Evidence-based patient information, patient decision aids, have been developed to assist patients with difficult health-related decisions. The rationale of evidence-based practice is to improve the quality of care through the identification and promotion of effective practice and elimination of practices that are ineffective or harmful. The practice of EBM involves five essential steps: converting information needs into an answerable question (PICO format); finding the best evidence to answer the question; critical appraisal of the evidence for its validity and usefulness; application of the results into clinical practice; and evaluating performance. The practice of EBM should be a part of patients' daily care.

Key words: Evidence-based medicine, Evidence-based practice, Evidence-based patient choice, Evidence-based physician-patient relationship, Patient decision aids.

Introduction

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of current best evidence (about therapy, prevention, etiology, harm, prognosis, diagnosis and economic analysis) in making decision about the care of individual patients (1).

The practice of evidence-based medicine is a systematic approach to clinical problem solving, which allows the integration of the best available research evidence with clinical expertise (defined as the proficiency and judgment that individual clinicians acquire through clinical practice) and patient values (defined as the unique preferences, concerns

and expectations, such as cultural and religious). It should be accompanied by the evidence-based patient choice. Evidence-based medicine is applied to improve quality of care through the identification and promotion of effective practice and the elimination of practices that are ineffective or harmful. Good physicians use both their own individual clinical expertise and the best available external evidence, because neither alone is enough (1-3). To make the right decision about patient's health care, physicians combine their individual knowledge, clinical experience, close cooperation with colleagues, and evidence-based tools, such as standard operating procedures, protocols, guidelines, algorithms, and current best evidence on the Internet. In addition to clinical expertise, a clinician must have compassion and good listening skills, to understand patients' illnesses in the context of their experience, personalities, and cultures. However, the experience relates to the past, and fast-developing science of medicine requires our orientation towards future, the last, newest, and most useful refinements of physicians' knowledge and practice. Keeping up-to-date with current best evidence is challenging, and requires a habit of looking for current best evidence as efficiently as possible (5).

Evidence-based clinical practice

The practice of evidence-based medicine requires the integration of individual clinical expertise and patient values with the best available clinical evidence from systematic research. Evidence-based health care means the application of the principles of evidence-based medicine to all professions associated with health care, including purchasing and management. Evidence-based health care should be accompanied by evidence-based patient choice, offering patients information about treatment alternatives, the benefits and harms, and empowering them in decision making (6). The practice of EBM involves five essential steps (Box 1).

Box 1 Five essential steps of EBM practice:

Step 1 converting information needs into an answerable question
Step 2 finding the best evidence to answer the question
Step 3 critically appraising the evidence for its validity and usefulness
Step 4 applying the results of the appraisal into clinical practice
Step 5 evaluating clinical performance

Physicians can incorporate best evidence into their evidence-based practice through two main modes: 1) the "doing" mode and 2) the "using" mode (2). In the "doing" mode physicians use at least the first four steps of evidence-based practice. In this mode, searches are restricted to freely available Internet resources that have not already undergone critical appraisal. So, physicians must invest time and effort for critical appraisal of articles for their validity and usefulness. After that, they can create an individual structured written summary of these first 3 steps - a "Critically Appraised Topics" or CAT. The aims of CATs are to summarize and consolidate physicians learning, make it cumulative, share it with others in the team, and refine physicians EBM skills. CATs have a number of limitations: they are based on quick searches for at least one useful article, therefore they are not a systematic review and practice guideline; might contain errors of calculation or appraisal judgments, and they become obsolete as soon as newer, better evidence becomes available. In the "using" mode, searches use evidence resources that have already undergone critical appraisal (eg, evidence summaries such as ACP Journal Club), thus skipping step 3. Unfortunately, most of pre-appraised resources are not freely available (2).

A. Step 1 of EBM practice: formulating an answerable clinical question

A clinician starts his or her search for the best and newest data needed to solve individual patient's problem by formulating an answerable clinical question. Good clinical question must be clear, directly focused on the problem, and answerable by searching the medical literature (1-4).

1 PICO format

A good clinical question should have **four** essential components structured in the **PICO** format (**P**atient or problem, **I**ntervention, **C**omparison, **O**utcome) (Box 2).

Box 2 PICO format:
- the **p**atient or problem – who are the relevant patients, what kind of problem we try to solve?
- the **i**ntervention – what is the management strategy, diagnostic test or exposure (drugs, diagnostic test, foods or surgical procedure)?
- **c**omparison of interventions – what is the control or alternative management strategy, test or exposure that we will compare?
- the **o**utcome – what are the patient-relevant consequences of the exposure in which we are interested?

2 Type of clinical question

The most common type of clinical question is about how to treat a disease or condition. Such questions are questions about intervention. The other types are: questions about intervention, questions about etiology and risk factors, questions about frequency and rate, questions about diagnosis, questions about prognosis and prediction, question about cost-effectiveness, and question about phenomena (4).

B. Step 2 of evidence-based medicine practice: finding the evidence

After formulating the clinical question, which stems from a concrete patient, the next step is to search for relevant evidence that will provide the answer to the question. Some research designs are more powerful than others in their ability to answer research questions. For each type of questions a systematic review of all the available studies is better than any individual study.

Important sources of evidence include *online electronic resources*. Physicians should use websites and texts that are revised at least once a year, select and appraise evidence in

Table 1 Levels of evidence and grade of recommendation for ranking the validity of studies about *therapy, prevention, etiology and harm,* Oxford Centre for Evidence-based Medicine*

Grade†	Level	*Therapy/prevention, etiology/harm*
	1a	Systematic review (SR) (with homogeneity) of randomized controlled trials (RCTs)
A	1b	Individual randomized controlled trial (RCT) (with narrow confidence interval)
	1c	All-or-none study‡
	2a	SR (with homogeneity) of cohort studies
	2b	Individual cohort study or low quality RCT(<80% follow-up)
B	2c	"Outcomes" research; ecological studies
	3a	SR (with homogeneity) of case-control studies
	3b	Individual case-control study
C	4	Case-series (and poor quality cohort and case-control studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

* Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.
† Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
‡ All-or-none study: when all patients died before the intervention became available, but some now survive on it; or when some patients died before the intervention became available, but none now die on it.

Table 2 Levels of evidence and grade of recommendation for ranking the validity of studies about *prognosis*, Oxford Centre for Evidence-based Medicine*

Grade†	Level	*Prognosis*
	1a	SR (with homogeneity) of inception cohort studies; or a clinical rule validated on a test set
A	1b	Individual inception cohort study with ≥ 80% follow-up; or a clinical rule validated in a single population
	1c	All-or-none case-series
	2a	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
	2b	Retrospective cohort study or follow-up of untreated control patients in an RCT; or clinical rule non validated on a test set
B	2c	"Outcomes" research
	3a	
	3b	
C	4	Case-series (and a poor quality prognostic cohort studies)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

*Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.
†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

Table 3 Levels of evidence and grade of recommendation for ranking the validity of studies about *diagnosis,* Oxford Centre for Evidence-based Medicine*

Grade†	Level	*Diagnosis*
	1a	SR (with homogeneity) of level 1 diagnostic studies; or a clinical rule validated on a test set
A	1b	Validating cohort study with good reference standards; or a clinical decision rule not validated on a second set of patients
	1c	Absolute SpPins and SnNouts‡
	2a	SR (with homogeneity) of level >2 diagnostic studies
	2b	Any of independent blind or objective comparison; study performed in a set of non-consecutive patients or confined to a narrow spectrum of study individuals (or both) all of whom have undergone both the diagnostic test and the reference standard; a diagnostic clinical rule not validated in a test set
B	2c	
	3a	SR (with homogeneity) of 3b and better studies
	3b	Non-consecutive study; or without consistently applied reference standards
C	4	Case-control study, poor or non-independent reference standard
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

*Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.
†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.
‡ An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

explicit way, and cite evidence in support of statements about clinical care (1-5).

1 Levels of evidence and grades of recommendation

The Oxford Centre for Evidence-based Medicine (www.cebm.net) recommended the levels of evidence for ranking the validity of studies about therapy, prevention, etiology, harm, prognosis, diagnosis and economic analyses and grades of recommendation for clinical guidelines (Tables 1-4). Recommendations based on this approach are made for an average patient and may need to be

Table 4 Levels of evidence and grade of recommendation for ranking the validity of studies about *economic and decision analyses,* Oxford Centre for Evidence-based Medicine*

Grade†	Level	*Economic and decision analyses*
A	1a	SR (with homogeneity) of level 1 economic studies
	1b	Analysis based on clinically sensible costs or alternatives; SR of evidence; and including multi-way sensitivity analyses
	1c	Absolute better-value or worse-value analyses
B	2a	SR (with homogeneity) of level >2 economic studies
	2b	Analyses based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
	2c	Audit or outcomes research
	3a	SR (with homogeneity) of 3b and better studies
	3b	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
C	4	Analysis with no sensitivity analysis
D	5	Expert opinion without explicit critical appraisal, or based on economic theory or first principles

*Produced by Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M; www.cebm.net.
†Grades of recommendation: **A** consistent level 1 studies; **B** consistent level 2 or 3 studies or extrapolations from level 1 studies; **C** level 4 studies or extrapolations from level 2 or 3 studies; **D** level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

modified in light of an individual patient's unique biology and preferences.

2 Sources of evidence

There are different web sources of evidence. The search for best evidence should begin by looking at the highest-level source available for the problem in question.

Evidence-based journals of secondary publication like ACP Journal Club; *http: // www.acpjc.org*, Evidence-Based Medicine; *http://ebm.bmjjournals.com*, Evidence-Based Mental Health; *http://ebmh.bmjjournals.com*, Evidence-based Obstetrics and Gynecology; *http://www.harcourt-international.com/journals/ebog*, Evidence-Based Nursing; *http://ebn.bmj.com*, select from the biomedical literature original and review articles, summarize them, and present comments by clinical experts (2, 4, 5).

There are several *online evidence-based databases* (Box 3).

The other databases are MEDLINE with version PubMed and *PubMed Clinical Queries* (National Library of Medicine free Internet MEDLINE database), TRIP database, and SUMSearch (Box 4).

Box 3 Evidence-based databases:
The Cochrane Library (through the Cochrane Collaboration, http://www.cochrane.org
- The Cochrane database of systematic reviews: a collection of full text systematic reviews of the effects of health care, presents the best evidence, abstracts of reviews are freely available; http://www.cochrane.org/reviews/index.htm
- The DARE: includes systematic reviews that have been published outside of the Cochrane collaboration, all quality-assesses and with structured summaries, freely available on the Web outside the Cochrane library through Centre for reviews and dissemination databases; *http://www.crd.york.ac.uk/crdweb*
- The Cochrane Controlled Trials Register (CENTRAL): a bibliography of some 200,000 controlled trials, not freely available

Clinical Evidence; http://www.clinicalevidence.com; not freely available
CRD database; http://www.crd.york.ac.uk/crdweb: freely available

Internet sources of *evidence-based clinical practice guidelines* are The National Guideline Clearinghouse (NGC) (http://www.guide-

Box 4 Other evidence-based databases (free access):
- PubMed Clinical Queries (http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.shtml): question-focused interface with filters for identifying most appropriate studies for the question about therapy, diagnosis, etiology, and prognosis
- SUMSearch (http://sumsearch.uthscsa.edu/): a meta-searching service
- TRIP Database (http://www.tripdatabase.com): filters results by evidence-based synopses, clinical question, systematic reviews, guidelines, core primary research, e-textbooks, medical images, and patient information leaflet

line.gov) and Primary Care Clinical Practice Guidelines *(http.//medicine.ucsf.edu/resources/guidelines/index.html)*.

3 The search strategy

The starting point in the search for answers depends on the type of question we have asked. For *questions about intervention*, the best evidence comes from a systematic review of RCTs. The best first choice is the Cochrane database of systematic reviews. If there is not a Cochrane systematic review, the DARE review is the next best evidence. If there is not a DARE review, the next choice is PubMed Clinical Queries. PubMed Clinical Queries are the choice for *questions other* than questions about intervention, as well as TRIP Database and SUMSearch. The basic principles of search strategy includes: 1) defining of appropriate keywords from the clinical question, 2) choosing a bibliographic database, and 3) combining keywords with Boolean operators (AND/OR/NOT) (4).

C. Step 3 of evidence-based medicine practice: appraising the evidence

The next step is to appraise the evidence for its validity and clinical usefulness. Critical appraisal is a process developed by biostatisticians and clinical epidemiologists for assessing trials. Research evidence may be appraised with regard to the three main areas: validity (Are the results of the study valid?), importance (What are the results?), and applicability to the patients (How can we apply these results to patient care?) (2-4).

There are several tools for appraising a research article. One of them was developed by the *Critical Appraisal Skills Programme (CASP)*, Oxford, UK. CASP aims to help individuals to develop the skills to find and make sense of research evidence, helping them to put knowledge into the practice. CASP provides appraisal tools in the form of questions to help in critical appraising of systematic reviews, randomized controlled trials, qualitative research studies, economic evaluation studies, cohort studies, case control studies, and diagnostic test studies. The CASP tools are simple, easy to use, and freely available on the Internet (http.//www.phru.nhs.uk/casp/critical_appraisal_tools.htm).

D. Step 4 of evidence-based medicine model: applying the evidence

After we decide that the evidence is valid and important, we have to decide whether the evidence can be applied to our individual patient. The evidence should be fully discussed with the patient. The decision also should take into account the potential side effects of the drug (does side effect outweigh its potential benefits in a particular patient), the cost and availability of that particular treatment in the hospital or practice. The questions that we should ask before the decision to apply the results of the study are (2-5):

1 Are the participants in the study similar enough to my patient?

Factors affecting this decision include the age, different risk profile (as many drugs have increasing adverse effects in the ageing population), co-morbidity that could affect drug interaction and adverse effects (eg, renal insufficiency), and compliance with treatment dosage and duration. An example

is a patient with myocardial infarction and bronchial asthma, who should receive a beta-blocker for the secondary prevention of myocardial infarction, but which is contraindicated in bronchial asthma.

2 Is the treatment available and is health care system prepared to fund it?
Some interventions may be unavailable (an example is the diagnostic procedure involving positron emission tomography/computed tomography). Some intervention may be expensive, and require approval from the Hospital Drug Committee (eg, therapy with rituximab for lymphoma or infliximab for resistant Crohn's disease).

3 What alternatives are available?
If there are alternative treatments or procedures that we could use, we need to decide which one is most the suitable for our patient, balancing the potential benefits and harms. An example is drug therapy for arterial hypertension (there are different groups of drugs for the treatment of this condition, with the same effect).

4 Do the potential side effects of the drug or procedure outweigh the benefits?
Some of the adverse effects may not be mentioned in trials, but may be very relevant to our patient (eg, mood disturbances, impotence). The invasiveness of a test or procedure may affect patient's willingness to participate.

5 Are the outcomes appropriate to the patient? Does the treatment conflict with the patient's values and expectations?
We must take account of what the patient thinks, once we have explained the risk and benefits of different treatment options. The outcomes that are important to us may not be of same importance to the patient, particularly where quality of life is concerned. An example is a terminal cancer patient, who rejects all therapy except palliative therapy, with pneumococcal pneumonia. Despite the fact that antibiotics may reduce symptoms and prolong his life, his values are such that he would prefer a rapid natural death.

To help in clinical decision making, there are practical clinical guidelines, protocols, and algorithms. The ultimate judgment regarding the care of a particular patient must be made by the healthcare provider and the patient in light of all circumstances presented by the patient. The responsible physician's judgment is paramount in managing patients. There are circumstances in which deviations from guidelines are appropriate.

E. Step 5 of evidence-based medicine model: evaluating clinical performance

It is important to keep records of our clinical questions, search results, and critical appraisal of evidence, to follow up patients, and to record (and publish) outcomes. Also, we need to ask whether we formulate answerable questions, find best evidence quickly, effectively appraise the evidence, and integrate clinical expertise and patient preferences and values with the evidence in a way that leads to a rational, acceptable management strategy. We need to evaluate our approach at frequent intervals and decide whether we need to improve any of the four steps discussed above. After a process of self-evaluating, we must look whether our clinical practice becomes better. Do we need new protocols or algorithms, better access to Internet sources, and new changes in organizational processes? After implementation of those changes, we must look if they have actually occurred (4). The practice of EBM involves a process of life-long, self-directed learning in which caring for patients creates the need for important information about clinical and other health care issues. The practice and teaching of EBM should be part of the daily care of patients.

Evidence-based physician-patient relationship

During the examination of a patient (eg, in general practice or in a hospital) we use our individual knowledge, clinical experience, team work, and evidence-based tools (protocols, guidelines and algorithms) to complete evidence-based information and solve the problem. When the problem is new and have not been answered in the guidelines, we must look for current best evidence in available Internet resources, using the first four (the *"doing"* mode) or three steps (the *"using"* mode) of evidence-based practice (2).

In the process of decision-making, physicians must incorporate patient values (preferences, concerns and expectations). The physician should discuss with the patient the harms and benefits of all available options, patient's treatment goals and risk tolerance, and than decide *together* about a course of action. For some of the patients and problems, discussion should involve the patient's family. Patients who wish to delegate decision-making to a doctor or family member would still be given the information that they want. Evidence-based health care should be accompanied by evidence-based patient choice. Because of that, physicians should explain to patients the possibility of finding evidence-based patient information and patient guidelines on the Internet. But not all patients have the skills or access to the computer resources, so that downloadable version of information or materials are needed. Examples of such evidence-based patient information are patient decision aids, which have been developed to assist patients with difficult health-related decisions. Available trials indicate that decision aids improve knowledge and realistic expectations, enhance active participation in decision making, lower decisional conflict, decrease the proportion of patients remaining undecided, and improve agreement between values and choice. These decision support tools help patients become more engaged in their healthcare, but do not provide medical advice or replace physicians care (7, 8).

Databases of patient decision aids have been made available to the public by several academic institutions (Box 5.)

Box 5 Online patient decision aids:

- Canadian Cochrane Collaboration Systematic Review team created two databases of patient decision aids;
  1 *Decision Aid* contains more than 500 patient decision aids at various stages of development (http://decisionaid.ohri.ca/cochinvent.php)
  2 *A-Z Global Inventory* of available and evaluated patient decision aids with links to their authors (http://decisionaid.ohri.ca/AZinvent.php).
- The *BMJ online Evidence-Based Rheumatology* textbook, containing downloadable patient decision aids and consumer summaries (http://www.blackwellpublishing.com/medicine/bmj/rheumatology/decaids.asp).

Treats to the evidence-based medicine, recent activities and solutions

Study publication bias and outcome reporting bias are two major factors already known that negatively influence on evidence-based medicine by overestimation the effect of the experimental treatment (9, 10). The International Committee of Medical Journals' (ICMJE) policy on mandatory registration of clinical trials and the most recent US legislation on mandatory registration of trial summative results, which came in effect on September 27, 2007, have made an important contribution to the transparency of clinical research (10-15). Also they will decrease publication and outcome reporting bias, and will speed the dissemination of trial information. Finaly, the revised Declaration of Helsinki (http://www.wma.net/e/policy/b3.htm) in two items elaborate registration in publicly available database and ethical obligation on publication of negative and inconclusive as well as positive results; item

19: „Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.“, and item 30: „Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.“

All those activities are promising for a good future of evidence-based medicine and clinical practice.

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Ten "must read" articles on physical child abuse

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Child abuse is a common problem worldwide, and affects all ages, both sexes and all races. The presentation of child abuse cases is extremely variable, and early and subtle cases are easily missed. There is a growing body of literature on the subject of child maltreatment; healthcare providers caring for young children need to familiarize themselves with this literature to aid them in the identification, evaluation, and management of these challenging patients. This article reviews ten key publications on the subject of physical child abuse.

Key words: Review article, Child, Physical abuse.

Introduction

Child abuse is a common and significant problem worldwide. Early, sometimes subtle presentations are easily missed or misdiagnosed, resulting in repeated and often escalating injury. All healthcare providers who care for children need to be aware of the spectrum of signs and symptoms in children with injuries resulting from child abuse. Familiarity with the literature on this important subject can provide objective data to help with the identification, evaluation, management, and decision making critical to caring for abused patients. While it would be impossible to include the entire child abuse literature in a single review, this article reviews ten publications, according to author's selection which have helped to sculpt the landscape of child abuse literature.

Bruising

1. Sugar NF, Taylor JA, Feldman KW. Bruises in Infants and Toddlers: Those who cruise rarely bruise. Arch Pediatr Adolesc Med. 1999;153:399-403

Description: This was a prospective evaluation of infants and toddlers presenting for well-child care at community primary care offices. A total of 973 children aged 1 day to 35 months were evaluated in the study. 20.9% of the patients had bruising on examination. Only 2/366 (0.6%) of patients under 6 months of age had a single bruise, and only 6/107(5.6%) of those 6 to 8 months of age had any bruising. The percentage of patients with bruising increased significantly after 9 months of age, so that nearly ½ of the patients had bruises by 18 months and the majority of patients over 24 months of age had bruises.

Key Point: Pre-ambulatory patients (prior to cruising) rarely have even a single bruise. Any patient who is not yet cruising with any bruising should be carefully examined and evaluated for causes of abnormal bruising, including child abuse and bleeding disorders.

2. Stephenson T, Bialas Y. Estimation of the age of bruising. Arch Dis Child 1996; 74:53-55.

Description: Fifty cases of known accidental bruising of varying ages (range 1 to 14 days) were photographed and reviewed by a blinded reviewer to describe the colors observed and estimate the age of the bruising based upon accepted schemes. The estimated age of bruising was correct in only 54% of cases. Red color was seen in bruises aged 1 through 7 days, yellow color was seen in bruises aged 2 through 12 days, green color was seen in bruises aged 3 through 14 days and all other colors were seen in bruises of any age.

Key Point: Aging of bruises is inexact, and evaluation of colors of bruises from photographs adds additional difficulty. The color change of bruises as they age is imprecise, and probably should not be used to attempt to time injuries precisely.

Head Injury

3. Jenny C, Hymel KP, Ritzen A, Reinert SE, Hay TC. Analysis of missed cases of abusive head trauma. JAMA 1999; 281:621-626.

Description: This landmark study evaluated cases of known abusive head trauma to determine the frequency with which this diagnosis had been missed in prior evaluations. Fifty four of 173 (31.2%) abused children with head injuries had been evaluated by at least one physician after the time of their initial head injury. The diagnosis was most frequently missed in those patients who were very young, Caucasian, from intact/two-parent families, and those who presented with vague complaints such as vomiting or irritability. The most common misdiagnoses for these patients included gastroenteritis or influenza, accidental head injury, and "rule out sepsis". Five of the 54 missed cases (9.3%) died as a result of their injuries, and the authors felt that four of these five deaths would have been preventable if abuse had been recognized earlier.

Key Point: Infants with abusive head trauma often present with vague and nonspecific symptoms such as vomiting and irritability, and are more likely than older abuse victims to have the diagnosis missed. Physician bias may lead to increased recognition of child abuse in patients who are minorities and those from single-parent homes. If the diagnosis of abuse is missed, repeat injury is common and fatal injuries may result.

4. Duhaime AC, Alario AJ, and Lewander WJ, et al. Head injury in very young children: mechanisms, injury types and ophthalmologic findings in 100 hospitalized patients younger than 2 years of age. Pediatrics 1992; 90:179-185.

Description: The authors prospectively evaluated 100 children less than 2 years of age admitted to the hospital for a head injury. They applied a "biomechanical profile" to evaluate fully the circumstances of the injury incident, performed a detailed physical examination, radiological examination, and fundoscopic examination. Families were interviewed regarding the injury event. 24% of

patients were classified as victims of abuse; of these patients, 8 presented with a history of a fall less than 4 feet, 2 with admitted assault, and 14 with no history of injury. 54% of abused patients, as compared to 33% of patients with accidental injuries, had intracranial hemorrhage. Retinal hemorrhages were found in 10 patients; 9 of these were victims of abuse. The only patient with retinal hemorrhages resulting from an accidental injury was a passenger in a high speed motor vehicle crash who died as a result of their injuries.

Key point: Child abuse is a common cause of severe head injury in young children, and these patients have a significantly higher rate of intracranial hemorrhage, retinal hemorrhage, and death. While retinal hemorrhages do occasionally occur from accidental trauma, this is rare and typically associated with massive trauma.

Fractures

5. Leventhal JM, Thomas SA, Rosenfield NS, Markowitz RI. Fracutes in young children: distinguishing child abuse from unintentional injuries. Is J Dis Child 1993; 147:87-92.

Description: This retrospective case series evaluated 215 children less than 3 years of age with 253 fractures over a 4 year period. The cases were rated as questionable, likely, definite abuse or accident after independent review by 2 clinicians, 2 radiologists, and then a consensus of the clinicians and radiologists reviewing each case together. They classified 24.2% of fractures in this series as abuse, 8.4% as unknown, and 67.4% as unintentional. All rib fractures (12) in the study were classified as being the result of abuse. Of extremity fractures, 82% of those in children less than 1 year of age were felt to be due to abuse; 83% of those children with long bone fractures due to abuse had at least 1 additional fracture. The authors found that cases with no history of trauma, a minor history with a significant fracture, a midshaft or metaphyseal humerus fracture, or a fracture under 1 year of age, were more likely to be the result of child abuse. Skeletal surveys were performed in 38% of patients and revealed additional fractures in 31% of cases.

Key point: Fractures occurring in children under 1 year of age should be carefully evaluated for the possibility of abuse. Additionally, in cases where there is either no history of trauma or only a minor trauma history, abuse should be considered. Skeletal surveys should be performed in any case of a fracture under 3 years of age where child abuse is being considered.

6. Cadzow SP, Armstrong KL. Rib fractures in infants: Red Alert. The clinical features, investigations and child protection outcomes. J Paediatr Child Health 2000;36: 322-326.

Description: This study was a retrospective review of all cases of rib fractures in children under 2 years of age over a 5-year period. Eighteen total infants were identified, with a total of 101 fractured ribs. Child abuse was the etiology of the rib fractures in 15 of the 18 cases (83%). The average age of the patients with abuse-related rib fractures was 16 weeks, as compared to 52 weeks in those with accidental rib fractures. Of the 3 patients with rib fractures not due to abuse, two were run over by cars and the third was a patient with end stage liver failure and osteopenia. Four of the eighteen abuse cases had rib fractures identified incidentally during evaluation for an unrelated indication, and four were identified during evaluation of possible abuse due to other injuries/concerns. A presenting history of trauma was present in only five of the fifteen abuse cases, four of which presented with a history of a fall from a height of less than 3 feet.

Key point: Rib fractures are uncommon injuries in infants and young children. In the absence of significant bone disease or mas-

sive trauma, rib fractures in this age group are highly suggestive of abuse.

Miscellaneous

7. Tarantino CA, Dowd MD, Murdock TC. Short vertical falls in infants. Pediatric Emergency Care 1999; 15:5-8.

Description: The authors performed a retrospective review of infants 10 months of age and younger presenting with a history of a short vertical fall (four feet or less). 167 patients were evaluated for a short fall over a 3 year period. These included falls from beds (55%), couches (16%), or other objects (10%), or being dropped from a caregiver's arms (20%). The majority (85%) of patients had minor or no injuries. Twelve patients had a skull fracture, and 2 patients had an intracranial hemorrhage. Both patients with intracranial hemorrhage were later determined to be victims of child abuse. Patients with significant injuries were significantly more likely to have been dropped by a caregiver, while 84% of those who rolled off of a couch, bed or other object had no injury or minor injuries.

Key point: Short vertical falls are unlikely to result in intracranial or other serious injuries, and consideration of abuse should occur in these cases.

8. Coant PN, Kornberg AE, Brody AS, Edwards-Holmes K. Markers for occult liver injury in cases of physical abuse in children. Pediatrics 1992; 89:274-278.

Description: This prospective study looked at the use of laboratory markers for abdominal trauma in patients being evaluated for possible child abuse. Forty-nine patients ranging from 1 month to 11 years of age with no signs of abdominal injury were evaluated. Levels of liver transaminases, lactate dehydrogenase, and amylase were performed, along with a urinalysis. Four patients had elevated transaminase levels and one also had an elevated amylase level; these four patients then had abdominal Computed Tomography performed. Three of these four patients had liver lacerations on CT.

Key point: Occult abdominal trauma in victims of abuse may be detected through the use of serum transaminase and amylase levels. Suspected abuse cases should have screening levels drawn and abdominal CT should be performed in those cases with elevated levels.

Imaging

9. Sane SM, Kleinman PK, Cohen RA, et al. Diagnostic imaging of child abuse. Statement from the Section of Radiology, American Academy of Pediatrics. Pediatrics 2000; 105:1345-1348.

Description/Key points: This policy statement provides proposed guidelines for imaging in cases of suspected abuse. Skeletal survey is mandatory in all cases of suspected child abuse under 2 years of age, and should be considered on an individual basis in older children. This should include AP views of all extremity segments (humeri, forearms, hands, femurs, lower legs and feet), 2 views of the skull and thorax, an AP view of the pelvis, and lateral views of the lumbar and cervical spine. A single-shot "babygram" is *NOT* acceptable screening for abuse-related fractures. The authors recommend the use of radionuclide bone scans on selected cases over 1 year of age; bone scan is more sensitive than plain films for rib fractures and periosteal elevation, but is more expensive than plain radiography and often requires sedation. Repeat skeletal survey 2 weeks after the initial injury increases the diagnostic yield of plain radiography without the additional cost and sedation required for bone scan. Computed Tomography of the head (without contrast) is recommended in all cases of abuse with suspected or known head injuries. Magnetic Resonance Imaging of the brain should be considered 5 to 7 days

after the initial injury to fully delineate the intracranial injuries. Computed Tomography (with intravenous contrast) of the abdomen or chest should be performed in those patients with signs, symptoms, or laboratory abnormalities suggesting abdominal or thoracic injuries.

10. Zimmerman S, Makoroff K, Care M, Thomas A, Shapiro R. Utility of follow-up skeletal surveys in suspected child physical abuse evaluations. Child Abuse and Neglect 2005; 29:1075-1083.

Description: The authors performed a prospective evaluation of 48 patients with suspected abuse-related injuries. Additional information was yielded in 22/48 (46%) patients, including 3 patients in whom the outcome of the case (abuse or non-abuse) was changed (6%). A total of 27 previously undetected fractures were identified on repeat imaging performed an average of 21 days after the initial evaluation. The additional fractures included 18 rib fractures, 4 scapular fractures, 1 tibial metaphyseal fracture, 1 femur metaphyseal fracture, 1 tibial fracture, 1 clavicular fracture, and 1 fibular fracture.

Key point: Repeat skeletal survey, performed 2-3 weeks after the initial survey, can add critical information to the evaluation of a suspected child abuse case. Additional fractures, particularly rib and metaphyseal fractures, can be identified, while questionable findings on the initial survey can be clarified.

Conclusion

This article lists and summarizes ten articles on child abuse which have provided major contributions to the field of pediatrics and the recognition and evaluation of suspected non-accidental trauma. All pediatric medical care providers should be familiar with these articles and incorporate the recommendations into their practice. Failure to recognize, completely evaluate and appropriately manage, or properly report child abuse is likely to result in repeat injury to the child and their siblings.

Regenerative medicine and embryonic stem cells: are there alternatives?

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Use of human embryonic stem (ES) cells in regenerative medicine is associated with ethical problems because these cells can only be obtained from human embryos generated outside the human body. A recent discovery suggests that human ES-like cells can be obtained without generating human embryos thus providing a problem free solution for regenerative medicine.

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Introduction

Regenerative medicine can be broadly defined as development of innovative therapeutic approaches that will enable the human body to repair and regenerate damaged cells, tissues or organs. Current scientific evidence favours the use of one specific cell type for therapy, namely human embryonic stem (ES) cells. These cells can only be obtained from human embryos generated outside the human body. Historical evidence suggests that experimentation on parts of human body will inevitably create ethical problems. As a result, the proposed use of ES cells in therapy is currently one of the most hotly contested areas of biomedical research. Some ethical issues associated with the use of ES cells in regenerative medicine will be highlighted here and recent scientific developments that can potentially eliminate ethical problems will be presented.

Stem cells are usually defined as cells capable of both self renewing and producing different cell types. On the basis of their potential to generate different cell types, stem cells are classified into several categories (Table 1). In mammalian organisms only zygote and early blastomere are totipotent. Totipotent cells can generate all cell lineages of an organism, including extra-embryonic tissue. Embryonic stem (ES) cells, on the other hand, are pluripotent and they can generate all cell types of the body in vivo and in vitro

Table 1 Classification of stem cells according to their developmental capacity

Potency	Developmental capacity	Cell type
Totipotent	All cell lineages including extra-embryonic tissue	Zygote and first cleavage blastomere
Pluripotent	All cell lineages but no extra-embryonic tissue	Embryonic stem cells
Multipotent	One cell lineage	Adult stem cells (e.g. hematopoietic cells which will produce all blood cells)
Unipotent	One cell type	Cells that produce terminally differentiated cells (e.g. spermatogonial stem cells which will produce sperm)

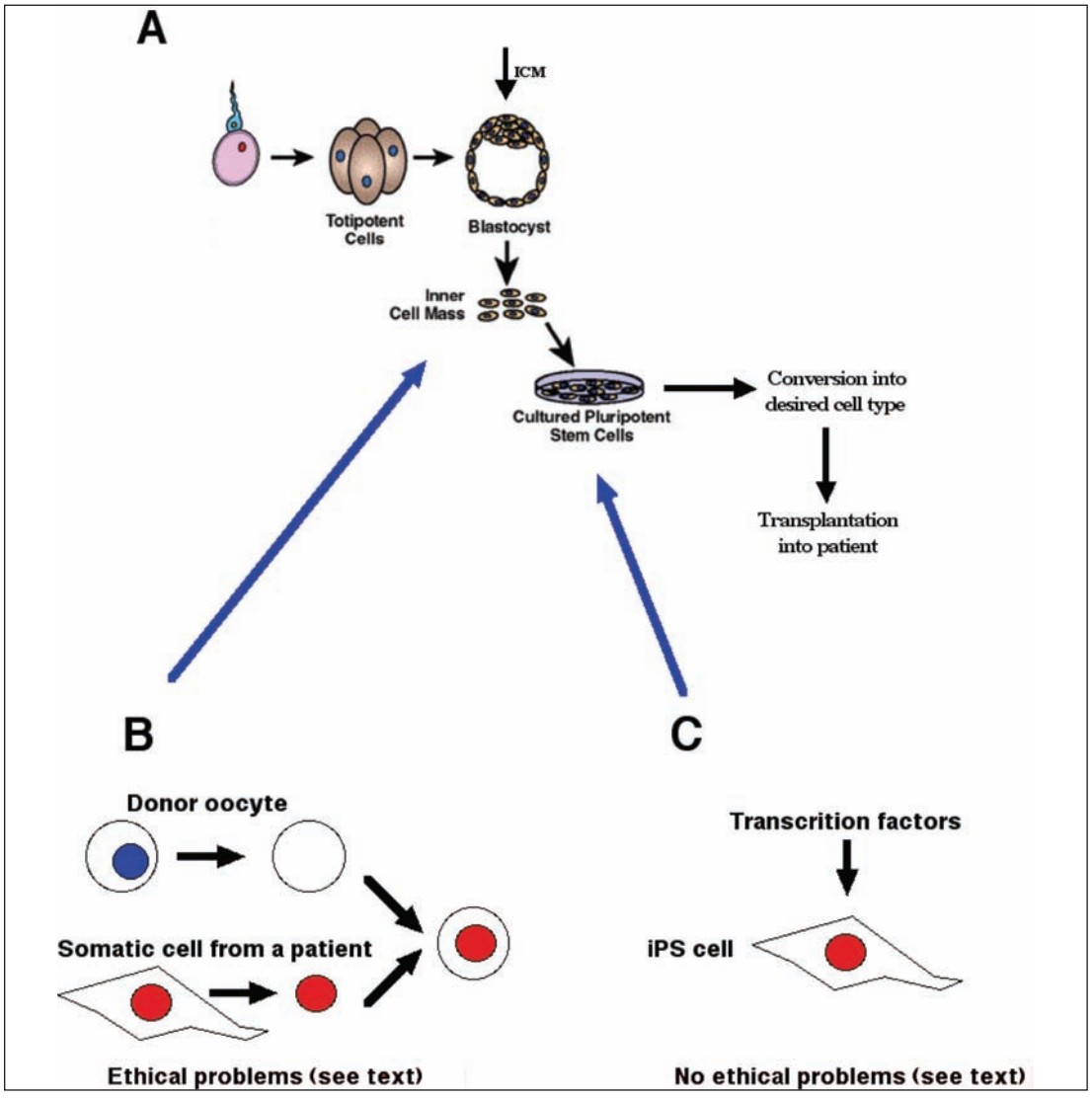

Figure 1 **A**. Isolation of human ES cells from human embryos. ES cells are depicted as Cultured Pluripotent Stem Cells. These cells should be converted into a desired cell type before transplantation into patients. ICM (Inner Cell Mass). **B**. Procedure for Somatic Cell Nuclear Transfer or therapeutic cloning. Nucleus removal from a donor oocyte and a patient somatic cell are depicted, as well as the subsequent insertion of the patient cell nucleus (red) into the enucleated donor oocyte. The resulting hybrid cell now has the same fate (blue arrow) as the naturally fertilized egg in panel A. ES cells obtained in this way are an exact genetic match for the patient. **C**. An iPS cell generated by cell reprogramming (addition of transcription factors into a somatic cell). The blue arrow indicates that iPS cells are equivalent to pluripotent stem cells and can be used in therapy.

but cannot generate extra embryonic tissue. Each tissue has a pool of adult stem cells which are multipotent and can generate all cell types of one lineage, for example hematopoietic cells. The ability of ES cells to generate all cell types of the body makes them a far more attractive target for regenerative medicine than adult stem cells. For example, ES cells can be experimentally induced to differentiate into any desired cell types (e.g. heart muscle cells) and then transplanted into damaged tissues/organs (e.g. heart) to fully regenerate them. Adult stem cells, on the other hand, are restricted to only one tissue type.

The proof of principle for the above ES cells-based theoretical framework which underpins regenerative medicine (Figure 1 A) already exists in the case of laboratory animals such as mice. For example, mice used as a model of Parkinson's disease (1) show significant improvement after transplantation of dopamine neuron cells, damaged in Parkinson disease, into the midbrain of Parkinsonian mice. Therapeutic dopamine neuron cells have been obtained from genetically matched mouse ES cell lines by somatic cell nuclear transfer (SCNT) followed by neural induction and differentiation into midbrain dopamine neurons (for details of SCNT see below). This promising animal study raises an important question: would the same approach work in humans? At present, there is no scientific reason to believe that it would not. However, as discussed above, ethical issues make the above approach questionable in humans.

Ethical issues

One of the major ethical and practical issues that seriously undermine the use of ES cells in regenerative medicine is the fact that human ES cells can only be obtained from human embryos. Human embryos can be generated outside the human body in *in vitro* fertilization (IVF) clinics during the course of infertility treatment. Unused fertilized eggs and/or unused donor oocytes that remain after IVF are the exclusive resources for generating human ES cell lines. A five day old human embryo, known as a blastocyst, has roughly 100 cells. Approximately 30% of blastocyst cells form the so called inner cell mass (ICM). ICM contains pluripotent ES cells (Figure 1 A). The standard procedure for generating ES cell lines includes removal of ICM from blastocysts and expansion of ES cells *in vitro* (Figure 1 A). The resulting ES cell lines can be stored indefinitely as therapeutic material. This procedure was successfully used for the first time in 1998 (2). In most countries it is permitted to generate ES cell lines for research. One of the rare exceptions is the US. The federal US government prohibits funding of scientific work that aims to create human ES cell lines. However, funding from non-governmental resources is allowed for this type of work.

A prerequisite for any successful regenerative therapy is that ES cells must be genetically matched to the patient in order to avoid tissue rejection. Exact genetic matching can only be achieved by using the patient's own cells. A laboratory technique known as SCNT, which was instrumental in generating the first cloned mammal, Dolly the sheep, is at present the only way to obtain genetically matched therapeutic ES cells (Figure 1 B). Scientists working in the field of regenerative medicine frequently refer to SCNT as therapeutic cloning. In this procedure a somatic cell (e.g. skin cell) is taken from a patient, the nucleus of this cell removed and inserted into a donor oocyte whose nucleus has also been removed (Figure 1 B). The resulting hybrid cell is allowed to divide to form a blastocyst from which ES cell lines will be obtained (Figure 1B). These ES cell lines are the exact genetic match for the patient's tissues, thus eliminating prob-

lems associated with tissue rejection. The ES cell lines can be used to obtain any single human cell type that may be required for therapy.

However, therapeutic cloning could inadvertently pave the way for reproductive cloning. Reproductive cloning can occur if the cloned blastocyst is allowed to be implanted into a uterus. The General Assembly of United Nations has officially adopted a document (The 2005 UN Declaration on Human Cloning) which calls upon all member countries to prohibit reproductive cloning. Some countries including the UK have allowed scientists to proceed with therapeutic cloning by issuing appropriate licences. All human embryos generated during the course of this procedure must be destroyed before they become 14 days old. However, in many countries therapeutic cloning has not been formally allowed yet.

In summary, the current theoretical framework behind regenerative medicine is almost entirely based on (a) human ES cell lines as the key therapeutic material and (b) therapeutic cloning as a way of preventing tissue rejection upon transplantation (Figure 1 A and B). This theoretical framework has both practical and ethical problems. Practical problems are highlighted by the fact that there is no unlimited supply of human oocytes or fertilized eggs required for therapeutic cloning. The key ethical problem is the danger that therapeutic cloning could be misused and attempts made for reproductive cloning in people.

Negative developments

The single event that added the greatest element of controversy to the already controversial field of human therapeutic cloning was the case of scientific fraud by the Seoul University research group led by Dr. Hwang Woo-Suk. In a scientific paper published in the prestigious journal Science Dr. Woo-Suk and his colleagues claimed that the above theoretical framework behind regenerative medicine (Figure 1) works in practice. In other words, they claimed success in transferring the human somatic cell nucleus into the human oocyte, propagating the resulting hybrid cell in vitro until the stage at which they were able to isolate human ES cells (blastocyst) and subsequently establishing human ES cell lines, perfect genetic matches for 11 different patients. However, detailed scrutiny of the published material by the scientific community raised some doubts about the authenticity of the published photographs of cultured ES cells. This led to a full investigation by the Seoul University which concluded that the entire study was fabricated. The published paper was eventually retracted by the journal Science and Dr. Woo-Sook was suspended. This case of scientific fraud seriously damaged the credibility of therapeutic cloning. Also, some scientists questioned whether therapeutic cloning will ever be practical, given problems such as its low success rate (see below).

At present, there is evidence that some aspects of human therapeutic cloning work in practice, namely production of cloned blastocysts (3). However, no human ES cell lines have been obtained yet from cloned blastocysts and future studies will show if this is possible. Recent developments in primates provide strong support for the notion that human therapeutic cloning will work in practice. For example, the journal Nature published a study last year in which scientists were able to verify therapeutic cloning for the first time in a species close to humans – rhesus monkeys (*Macaca mulatta*) (4). The research group led by Shoukhrat Mitalipov from Oregon National Primate Research Centre used several hundred monkey oocytes to obtain 35 cloned blastocysts. In order to generate ES cell lines the 20 best cloned blastocysts were selected resulting in 2 monkey ES cell lines. It is not difficult to

spot the major problem here: the low success rate of therapeutic cloning in primates. Although Mitalipov's study used an improved procedure for therapeutic cloning the success rate of this technique (oocyte to ES cell line ratio) is still extremely low. In order to obtain 2 ES cell lines Mitalipov and colleagues used a total of 304 oocytes (0.7% success rate). This is a serious practical problem which becomes ethically questionable in the context of human therapeutic cloning. For example, if the success rate of therapeutic cloning in humans is similar to that of monkeys, and without significant improvements, many oocyte donors may be required to produce a single genetically matched ES cell line for a single patient.

Are there alternatives to human therapeutic cloning?

Given the success with therapeutic cloning in Parkinsonian mice and their significant improvement after transplantation of ES cell-derived dopamine neurons into their midbrains (see above) and clear indications that human cloned blastocysts can be generated (3) some scientists argue that it is still worth pursuing human therapeutic cloning. However, it is also reasonable to search for alternative approaches that may eliminate the ethical problems discussed.

Modifications of therapeutic cloning have recently been developed in order to address some of the ethical problems. For example, Meissner and Jaensich from MIT developed a technique in mice which prevents implantation of a cloned blastocyst into the uterus (5). If this technique is replicated in humans it would essentially prevent the use of cloned blastocysts for reproductive cloning. However, it is likely that the technique will be difficult to implement in human oocytes because they are sensitive to experimental treatments. More recently, scientists in the UK have applied for a licence to create animal-human hybrid embryos by using animal instead of human oocytes. In September 2007 the UK Human Fertilization and Embryology Authority approved these applications. By using animal oocytes the problem of large numbers of human oocyte donors required for therapeutic cloning can certainly be eliminated. However, creation of animal-human hybrid embryos raises further ethical concerns and causes new problems e.g. whether animal viruses can spread into the human genome.

These proposals are only minor amendments of the present technology for therapeutic cloning and none of them really provide problem-free solutions to serious ethical issues raised by therapeutic cloning. Ethical problems can be fully eliminated only by providing source(s) of therapeutic cells which do not originate from human embryos. A reasonable alternative is the use of human adult stem cells which are present in small numbers in each adult tissue. However, these cells have limited developmental potential (see Table 1). In addition, raising a sufficient number of adult stem cells for therapy may not be practical. An alternative scenario would be reprogramming somatic human cells in order to convert them into cells which will have the properties of human ES cells. Is this possible?

Many scientists have been trying to develop protocols that could convert somatic cells into ES-like cells but without much success. However, after painstaking work, the Japanese scientist Shinya Yamanka and his PhD student Kazuthosi Takahashi from Kyoto University have recently been able to reprogram mouse somatic cells so that they essentially become cells with all the major characteristics of mouse ES cells (6). They managed this by simply introducing four transcription factors into mouse somatic cells: Oct3/4, Sox2, c-myc and Klf4. Apparently, these factors alter the genetic programme of mouse somatic cells and lead

them to dedifferentiate and become ES-like. To make them distinct from ES cells, reprogrammed cells are now called iPS (induced pluripotent stem) cells. This important discovery led Yamanaka to try the same procedure with human cells. Not surprisingly, Yamanaka and colleagues have been able to generate human iPS cells from human skin fibroblasts, using the same combination of transcription factors as in the case of mouse cell reprogramming (7). In addition, a research group led by James Thompson from Wisconsin University reproduced Yamanaka's results and obtained human iPS cells using a slightly different combination of transcription factors (8). Tests have shown that human iPS cells have all the major characteristics of human ES cells including self-renewal and pluripotency, suggesting that iPS cells may be suitable for therapy.

Taken together, studies by Yamanaka, Thompson and their colleagues unequivocally show that human somatic cells can be converted into ES like cells. Many scientists now believe that iPS cells constitute a superior option for regenerative medicine in comparison with therapeutic cloning-generated ES cells because the iPS cell technology is free from major ethical problems (Figure 1 C). For example, Dr Ian Wilmut, credited as the scientist behind creation of Dolly the sheep and the pioneer of therapeutic cloning, has recently abandoned therapeutic cloning in favour of iPS cells. In addition, many US and European laboratories are switching their work to iPS cells. However, there are still some unanswered questions that must be addressed before iPS cells can be used in therapy. For example, iPS cells contain viruses which are used for introduction of transcription factors. Some of these viruses may cause tumorigenicity of iPS cells after transplantation into patient bodies. In addition, one of the transcription factors originally used to reprogram human skin cells by Yamanka's team is c-myc, an oncogene. Oncogenes are genes that promote tumour growth suggesting that the presence of this transcription factors may increase the risk of tumour formation by therapeutic cells. However, Yamanaka's team have recently managed to reprogram human skin cells without the c-myc transcription factor (9). It is also possible to select viruses for introduction of transcription factors that will be harmless to humans, thus eliminating problems of tumorigenicity.

Do the above developments mean the end of therapeutic cloning? Not necessarily. Proponents of therapeutic cloning believe that it still represents a viable option for therapy. Their main argument is that iPS cells are not 100% equivalent to ES cells and until it is unequivocally proven that iPS cells are safe for therapy in humans the work on human therapeutic cloning should continue. This is understandable since human ES cells represent the golden standard against which all potentially therapeutic cells should be measured. However, one thing is clear. There is now a hope that in the near future the technology for production of therapeutic cells in regenerative medicine will be free from the ethical problems that undermine therapeutic cloning.

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The nightmares of a middle-aged editor

Richard Horton

It was an inspirational moment for me when I first came to Croatia, building friendships with the editors of the *Croatian Medical Journal*, friendship and relationships which are even stronger today than they were a decade ago. And it is a particular pleasure to be able to be back to see my friends here and to have the opportunity to reflect a little bit on the world of knowledge, research, education, and how editors and the scientific community fit in to this emerging culture. As I say, it was a decade ago since I first visited Croatia, and that was a remarkable moment, not just an opportunity to watch personally a country emerging and growing out of an extraordinary difficult time, but it was also a moment to see a people reborn out of a moment of struggle towards an astonishing period of liberty and the impact that that liberty had on all aspects of your society. The 1990s were a moment of hope and optimism, but it is too easy to forget the human and the historical scars that run deep, even in a country that is as safe in its democracy as Croatia. But sometimes the wounds are still fresh – like a newspaper article that appeared in a daily paper in the UK – the *Guardian* – only in March of this year, where somebody who had taken part in an atrocity inflicted against your country had astonishingly escaped and taken up residence in the United Kingdom, and was discovered. So, these wounds which we had hoped could be healed will from time to time be inflicted again. And that is very painful, because it forces us to ask what have been the sacrifices that you have made, what those sacrifices have been for. What was it that you fought for in the 1990s – for your independence? What was and what remains the objective of your society and how will your children, our children, judge our behaviour today. How will they write a report card on our actions as we are living them right now?

2008 is a very important year in the world of science and medicine and it is important for two specific anniversaries. It is the 60th anniversary of the founding of the World Health Organization, a moment in history when the world came together to build a better place for health and well-being, and it is also the 60th anniversary of the writing of the Universal Declaration of Human Rights. And both, the constitution of the World Health Organization and the Universal Declaration of Human Rights, enshrine the notion of the right to health, a very important right that we hold dear to us in democratic

After permission from Croatian Medical Journal, additional web material to the article Marušić M. Richard Horton, editor of *The Lancet*, visits Croatia to support the *Croatian Medical Journal. Croat Med J. 2008;49(3):422.*

nations. What is that right about? In Europe the notion of human rights has a long and distinguished, although occasionally bloody, history. There have been three critical turning points in the European history and the story of the progressive realization of human rights. If I may be momentarily immodest and say that perhaps the first of those was in the 13th century in Britain with the writing of the Magna Charta and the enshrining of the right to *habeas corpus*, that is to say, a fair trial, legalizing for the first time in European culture, modern European culture, the notion of justice, protecting the individual from arbitrary judgement, the principle that we still hold dear, I hope, to this day. In the 18th century came the French revolution, characterized by terrible violence but also symbolizing again a moment of extraordinary European enlightenment. The French encyclopaedists, perhaps some of the first editors of our modern time, gathered and ordered human knowledge, not just for the sake of knowledge, but with the expressed purpose of applying knowledge for society's improvement, the social reform. And that triggered a generation of writers, such as Mary Wollstonecraft in England, who defended and advanced the rights of women and men, the idea that liberty is a crucial human value that we should protect in our society. And the third turning point was a global phenomenon in the 20th century after the Second World War when we created mechanisms through the United Nations, World Health Organization, and the Universal Declaration of Human Rights, that symbolized the contribution of human knowledge, the importance of human rights and liberty, and the ways those ideas could again contribute to social progress.

Now I am truly middle-aged. I am 46 years old, as my daughter repeatedly tells me, and I am the editor of just one of many thousands of journals. But I sit at the intersection between two worlds – the public world and the professional world, and my job, as is the case for all editors, is to mediate a conversation, although largely within a professional world. It is a world in which the public is increasingly not only a spectator, but also a participant. But, at the same time as we are reflecting on the place of knowledge in a society and the role of an editor as a student of knowledge, we might also ask ourselves why our governments should invest in science, research, and knowledge.

Why should the minister care about the future of Croatian education and science? And my answers to that question go to the heart of what it is to believe in a good society. At some deep level, our society believes that research and knowledge contribute positively to social progress. We believe in the liberty of ideas as the best means to foster and strengthen social justice, from Magna Charta to the enlightenment, to modern advanced democracies and the way we think about human knowledge. And we believe in protecting and advancing human life and human values, guarded as they are by health system that protects life and, equally important, by university and education system that protects the values we hold most dear, the values we fight for, that we sacrifice, sometimes, our lives for. These are our secular temples in our scholarly culture. The task of an editor of a scientific journal is, let me be very frank and modest, it is to respect the history of human inquiry, to respect the values of liberty and dissent, integrity and independence. It is to strengthen the culture of scholarly fluency, the perpetual tacking that takes place between competing visions of the truth until we arrive at an agreement that represents the best that we can say about the nature of the world and the best that we can say of one another as fellow human beings. Editors have a role in mediating this dialectics, this public reasoning in a spirit of robust, rigorous, and honest exchange.

My proposition today is that we face a moral and intellectual crisis in our scholarly world. It is the crisis that threatens to undermine two thousand years of gradual human improvement towards a just society. It is a set of realizable rights that we have been striving for, which includes the right to health, and it is these rights that are in jeopardy. The task of intellectuals, the task of every one of you in this room today is to diagnose accurately this crisis. It is to dissect it, to anatomize it, to characterize its pathology, to define the causal pathways of its disease processes, and to design remedies not only to palliate it but also to defeat the agent that threatens the integrity of our scholarly body. Because, if our intellectual communities become infected with diseases of corruption, fear, oppression, and psychological violence, the moral compass, the progress of our entire society, will be fatally corroded – to the point where human atrocities will be allowed to flourish again.

I want to show you a title of an article in the *JAMA*, edited by our colleague Catherine DeAngelis, which talks about impugning the integrity of medical science. That is the subject of today's concern. And the nature of this crisis runs deep and affects many of us. All countries are affected by this; all scholarly communities are affected by this. The responsibility to defeat this crisis rests with all of us, between nations, among nations.

In this particular case we have an example of a paper, and this was the draft planned for submission to *JAMA*, where there is an authorship list with a query for an external author. In other words, this paper was drafted by a ghost-writer and that paper was then put out to tender and the highest bidder, the person who could be the most influential, in a sense the person who could represent the article from the perspective that the sponsor wanted it to be represented, could be then put in the first author position. The authorship as it finally appeared in the paper as published included such a person at the first author position. Here is an example of corrupt authorship practice that affected one of the most significant journals in the medical domain. And it also affected loads of us in the UK, when a very well known media psychiatrist was accused of plagiarism, the dean dismissed from a University in the UK – a very senior member of academic community, because of his breach of scientific integrity and research misconduct.

It affects *The Lancet* as well, we are not immune from this and I do not pretend we are. We published a comment piece in December last year, entitled Ten Myths and One Truth about Generalised HIV Epidemics. The first sentence runs: "Despite substantial progress against AIDS worldwide we are still losing ground," and the article is signed by James Shelton. That article then appeared again, under a different authorship: "Despite substantial progress against AIDS worldwide we are still losing ground." And if you compare word for word, the article is identical, and what this website did and what this individual did was simply take the piece published in *The Lancet*, change the authorship and republish it on a website. We did not notice it; it was noticed by a third party who drew it to our attention.

Only this week, I am afraid to say, we had to issue an expression of concern about a research paper from a hitherto respected research group in Austria, because there were questions about the nature of informed consent and ethics approval of a work we published last year. This is ever present with us, almost on a weekly basis.

At *The Lancet*, we have been informed of another alleged breach of research integrity. I want to spend a moment talking about one particular case that has had a huge impact on us and is casting uncertainty and doubt about some of the most fundamental processes that we do at *The Lancet*, and they have affected all journals, not just us. We

published a paper a couple of years ago, by a leading Norwegian researcher called Jon Sudbø. It was a case control study, looking at patients with oral cancer, comparing them with controls and looking at the risk of cancer when you took a history of previous non-steroidal anti-inflammatory drug use (NSAID). What it showed was a remarkable result that the hazard ratio for NSAID use was halved, in other words, perhaps this drug was having a hugely beneficial effect on the risk of oral cancer.

In the process of peer review, our statistician recommended acceptance after a revision, concluding that this was a well-conducted study, a thorough statistical analysis. The first expert reviewer recommended only a minor revision and said it succeeded by a large amount – "a well conceived case-control study" – this reviewer said – "strong, well written, worthy of considering for publication in a journal such as *The Lancet*, they should be commended on writing a very sound piece of work." A second expert was a little more cautious and recommended major revision – "provocative, raises important issues but does not present them very well," and a third expert recommended rejection for failing by moderate amount; the reviewer also raised many questions, including the nature of one of the databases. This paper was submitted in September 2005. It was put through peer review, fast track, because the result was dramatic; revised, accepted, and published in October 2005. We had no reason at the time to suspect anything was wrong, but – there was something very badly wrong.

The wife of the prime-minister of Norway, Camilla Stoltenberg, is a public health researcher and over the 2005 Christmas holidays she read a whole series of papers for a review she was writing about this particular issue. And on top of her pile of papers was the first-authored paper by Jon Sudbø. As she sat down over Christmas vacation to read it, she was horrified, because she knew instantly as she read the paper that it could not be true.

In January 2006 she broke the story, she revealed her concerns about the integrity of the work and she asked this question: "How many people have truly read this paper, how could it appear in a supposedly high-quality medical journal when it was so obviously flawed?"

For a start, a lot of money was involved: Jon Sudbø has just got a 13 million dollar grant from the National Institutes of Health to continue his work, partly based upon the paper published in *The Lancet*. A lot of cash was at stake and then the story broke. And, of course, who was the subject of criticism? Was it the researcher? No, it was the editor. How could the editor be so stupid? How could the editor of a respected scientific journal make such a fundamental error of judgment to publish a piece of worthless research that the wife of the prime minister could spot in an instant when she sat down and read it? "Is *The Lancet* more interested in great headlines than good science?" – I was asked. "How often have you been warned about flawed research? Why didn't you listen to your peer reviewers? Don't you as an editor have a responsibility to protect the scientific record? Don't you as an editor have a responsibility to blow the whistle on bad scientific practice? Don't you as an editor have a duty to the wide public that funds the medical research to act responsibly?" These were the questions that have been put to me, quite fairly, quite rightly. And I struggled to provide good answers to those questions.

This scandal took in many institutions across Norway, not just the research institute of the hospital in Oslo; it affected databases of a multitude of other institutions. It affected the *New England Journal of Medicine* because Jon Sudbø has published some of his early papers there. Two papers had to eventually be retracted because Jeff Dra-

zen, the editor of the *New England Journal of Medicine*, also did spot the imperfections that lead him to question the decisions of his colleagues back in 2001 and 2004. The US connection spread the stain of research misconduct: it was not just *The Lancet*, it was not just the Norwegian institutions, it was not just the *New England Journal of Medicine*, and it was not just some of the institutions in the US which have collaborated with Jon Sudbø.

What were the Norwegians to do? Should they shut this up? Should they bury this case? Should they somehow sweep it under the carpet and hope it would go away? Should they try and protect their national pride by ignoring this problem? Which was in many ways for them an easy thing to do? Norway is a small country, five million people, intensely proud of its research tradition, a relatively young country, only gaining its independence in the early part of the 20th century. It had a lot to lose by letting this scandal envelope it. But what they did was the right thing. They set up an independent commission chaired by a Swede, and if you are a Norwegian you know how controversial that is to allow a Swede to chair an investigation about Norway – that is tantamount to revolution! But they asked Anders Ekbom, professor of epidemiology at the Karolinska Institute to come in and investigate what had gone wrong in Norway. He wrote to me very quickly after he was appointed, to say sourly that the paper we have published was indeed fraudulent and he recommended that we retract it. The worst thing an editor could do is to be forced into a situation where they have to admit their mistake and retract a paper. But it is the right thing to do sometimes. And on this occasion it was what we had to do.

Anders Ekbom gave a press conference, announcing the results of this investigation. Sixteen of 38 papers had to be retracted across 11 journals. He cited which those papers were, he named the journals, and he named the individual papers. It was a stain that spread far and wide. But this was the only way to clean up the stain that has affected Norwegian science. It was a tough thing to do but it was the right thing to do. And there is a set of lessons that have to be learned – that the line between error and incompetence and fraud is sometimes hard to draw; that when fraud is discovered it does throw doubt on an entire body of work, which places a terrible responsibility on the scientific community to investigate that body of work; that the risk is greater when one person controls the flow of information, as was the case of Jon Sudbø; and that fraud investigations are not easy, they are difficult – sometimes the documents disappear and sometimes we go back in time when it is hard to trace motivations and responsibilities.

Why was this fraud not detected earlier? Because Sudbø's work was so elegant, it was bewitching, we all wanted to believe it, including the editors and reviewers, because nobody suspects an individual, a colleague whom one works with every day, could truly be guilty of fraud. Jon Sudbø enjoyed what was called a boundless trust of his colleagues. The co-authors, because they trusted him, were disabled; they were not able to answer the tough questions. This was sensational research and – who is going to challenge sensational research? But, many of us should have acted earlier, and that includes me. Bad cases, unfortunately, do make bad law, but we all had a responsibility, particularly the supervisor of Jon Sudbø. Supervisors are there to inspire, to support, to advise, to assist, to guide, comment, and discuss, but also to act as accountability mechanisms, to monitor the quality of the work that has taken place.

When this investigation was finished and Prof Ekbom left Norway, it was clear that we all had a lot to learn. The institutions needed to do a better job in Norway at implement-

ing their existing rules, they needed to strengthen the mechanisms of supervision and internal audit and they needed to improve the procedures for noting errors, for example by pointing at independent audit. *The Lancet* had problems too. We had to do better. We needed to improve the rules by which we judge the authors and we needed to reconsider some of our peer-review processes. Should we really be fast tracking papers, even if those papers seem to be reporting an important finding?

Of course, these issues do not just affect *The Lancet*, as I said. One of the most famous scandals that hit basic science was around cloning, the Hwang case, and this hit one of the most respected scientific journals of all – *Science*. And real credit goes to *Science* here, because in situation where some of their papers were threatened with retraction what did the editor do? Did the editor try and bury this case, to move around it, to ignore it? No! Don Kennedy did not. Don Kennedy incredibly bravely again set up an independent commission outside the journal to investigate the journal's practices. And the conclusion of the independent commission was that Hwang's laboratories did not possess the patients' specific stem cell lines nor had any other scientific basis for claiming what he did claim for his cell clones. The result was that Don Kennedy had to retract those papers.

The role of an editor does not just extend to scientific journals. It is also important that the editor takes part in the public debate. This is the public role of an editor. Because we are responsible for the scientific record and because the money spent on research is tax payers' money so often, we have a duty, uncomfortable as it is, to sometimes step into the public realm and explain ourselves, to justify our decisions, to explain to the public why and how something is going wrong. That is an uncomfortable place to be, but occasionally one has to do it. I think that the lesson that came from the cloning fraud – this is what I wrote in the *Guardian* in 2006 – was that actually this was not a terrible defeat for science. This was a success for science! Not a failure! Why? Because science – and this is the great, wonderful thing about our scholarly community – science has quickly rooted out a fabrication of staggering proportions and was able to correct instantly the scientific record. That is to science's credit, not to its shame. Can you think of many other areas in society that when a fraud is discovered, or misconduct is discovered, the community instantly reassembles around the truth? That is an incredible strength of the community that we are in.

Science inquiry that Don Kennedy launched pointed out some of the perverse incentives that, unfortunately, we have to live by. *Science* and *Nature* have reached a special status, they concluded. Publication has a significance that goes beyond that of normal publication. The values such as and publishing in *Science* including enhanced reputation, visibility, position, or even cash reward, is sufficiently high that some may not adhere to the usual scientific standards in order to achieve publication.

So, we have set up a system that works well in competitive science but there is also a downside where perverse incentives can encourage some people to breach the incredible trust that our community puts in them. So what should editors do? A newspaper headline from the *International Herald Tribune* after the stem cell scandal urged tighter rules for science publications. We need to be vigilant, we must not throw the system of trust out, but we must be vigilant and re-stratify things. We have to clarify the roles that all authors play in the research and we should make data available for independent scrutiny, and we need to work together. We are a global scientific community, not just a national scientific community. You might think of your national journals as

being purely national journals, but actually your journals, your community, the editors of your journals are part of an international community. The great strength of that community is that we must find the ways to work together more closely. But there are some difficult lessons. Perhaps we should slow the peer review process down, take time to think more carefully about the work we publish, identify high risk papers, raise the bar for publication, and increase our level of suspicion. Maybe we should follow the example of clinical trials for all research and insist on data and safety monitoring boards that independently assess all research studies, creating checks and balances in research, with a greater oversight of research, one that does not exist today. Maybe we need to change the culture of our research institutions, but – not more rules! I do not want to see bureaucracy around research, but values – what we value about our research community – honesty, integrity, independence. Those are the values that need to be inculcated in everybody – from school students to the most senior emeritus professor. A research career implies duties as well as freedoms and it stands to all aspects of education training and mentorship. We need to reward the total life of a scientist, the way they live their life, not just their publications.

Perhaps we should reject the current process of peer review. If there is discord between reviewers maybe we should stop and pause and think again. Maybe we should demand agreement amongst reviewers; maybe we should not take at face value some responses from authors. If authors do not like what the reviewers say we should not ignore those reviewers. We should promote a dialogue between the author and a reviewer, respecting both but holding the author accountable for his or her statements. A less sympathetic approach to authors would reduce the risk of future retraction. Do not let authors bully you is one lesson from the Sudbø affair that I could take home. And also, take authorship more seriously: we should only give credit to authors when they have made a genuine, serious, and substantial contribution to science because every single author has the responsibility to check the integrity of his or her colleagues.

If we had done these things at *The Lancet*, we would not have had to retract the Sudbø paper because we would never have published it. So I take these lessons to heart. These are the errors that I am guilty of. My proposition to you is that the lessons that *The Lancet* has gone through apply beyond *The Lancet*. They apply, I think, to many other journals.

But we do need to think about these perverse incentives. In the case of Eric Poehlman in the US, when he was caught out of the fraud, he said: "I believe that it was okay to misrepresent minor pieces of data to increase the odds that my grant would be awarded." That is the culture we are promoting in science! "The structure of the University of Vermont" – he said, "created pressures which I should have but was not able to stand up to." Why? Because the values in that institution were not strong enough. He was allowed to get away with subverting the integrity of science in that institution. Poehlman went to prison for his breach of research integrity.

In the UK we tried to create light-touch mechanisms – the Committee of Publication Ethics and the Panel for Health and Biomedical Research Integrity – to offer support to institutions and journals when they face episodes of alleged scientific misconduct, because misconduct occurs in many different ways.

In a study of 500 randomized trials from 2000, different elements of what makes a good clinical trial were assessed, such as allocation concealment, randomization, doing the power calculation. And in many of these trials these data were simply not reported

– 82% not reporting allocation concealment, 79% how randomization took place. What they concluded in this paper was that "poor reporting of methodological characteristics will prevent reliable quality assessment of many published trials, so research misconduct is not just inventing data, it is doing bad science." And that is where we have such an important role in supporting good science. Three quarters of papers were not reporting fully efficacy outcomes, two thirds not reporting harms, and so on. The medical literature, therefore, represents a selective, biased subset of studied outcomes. It is as much a concern for research integrity as outright fraud. When over 3000 NIH-funded scientists, some of the best scientists in the world were polled, 16% said that they have seen or been involved in changing results or design after pressure from a sponsor, more than one in ten reported fraudulent or questionable interpretation of data and 6% failed to present data that contradicted one's past work. In this paper in Nature they concluded: "Our evidence suggests that mundane regular misbehaviours present a greater threat to the scientific enterprise than those caused by high-profile misconduct cases, such as fraud." And some journals have reacted. To the great credit of the *New England Journal of Medicine*, they expressed concern about inaccuracies in data in a clinical trial they published. The authors came back immediately in this terrible row between editors and the scientists and said "we stand by our original data." The editors responded again, bravely in my view, and said that the authors were not accurate in their presentation and that they (editors) continued to issue their expressions of concern around this very significant clinical trial.

What is the solution? In the world of clinical trials, one solution is to try and register those trials, to set up a mechanism whereby people say what they are going to do before they do it and then you hold them accountable after they have done it. International Committee of Medical Journal Editors has issued guidance on sponsorship, authorship, and accountability and clinical trial registration to try to strengthen this culture, these values that are so important to research integrity. We can do research into the way journals and science operates: peer review, authorship, fraud, bias, communication, and quality control. All of these areas are subject to research and the editors of your own journals could make important contributions to our knowledge about the way journals work. We need to come out with an open debate, open the culture of debate about research integrity and not be frightened of discussing this.

We need to think more about defining what we can do to prevent fraud, how we implement guidelines, how institutions should work at promoting research integrity, how we do investigations of fraud and protect whistle-blowers, and how we reform the academic reward system so that we try and get rid of some of these perverse incentives.

Think about codes, such as Hippocratic Oath. Do we need Hippocratic Oath for science? In the UK, the Council for Science and Technology has promoted a code for scientists – rigor, respect, and responsibility – a universal ethical code for scientists where rigor, honesty, and integrity are fundamental values for every scientist – the respect for life, the law, and the public word, responsible communication, listening, and informing. These are the values that we have to uphold. What can we do to uphold those values?

Now I come to a difficult issue. When I opened my copy of *Science* a few weeks ago I was confronted by this article: Croatian Editors Fight with the Medical School over Journal's Fate. It is difficult for me to talk about this because it makes me incredibly distressed to read reports in respected international scientific journals about one particular dispute in Croatian science, which

has dominated discussions in European and now North-American publications. Not just discussion about two editors and a journal but also, unfortunately, reflecting on the culture, the values that I have been talking about so far.

Let me be very clear about where I stand on this, because I do not want to be misunderstood. Professor Ana Marušić and Professor Matko Marušić are my respected colleagues and friends. They are to me international symbols of not only Croatia's scientific and medical success, but also Croatia's national success during and since your country's independence. Their stories, their lives mirror, to my mind, Croatia's rebirth as a nation. Their values, which I know very well, personally and professionally, are Croatia's great strengths of integrity and excellence. They are some of the most fabulous ambassadors to your nation whom I have known, and their journal, the *Croatian Medical Journal*, amplifies the reputation of Croatian medicine and medical research well beyond Croatia's borders.

All of which is to say, the reading of what has taken place in the past few years in an article in Science to the journal and to Professors Marušić is a story that I do not think I could have made up, and nobody would believe me if I had made up. Accusations that go to the heart of their personal integrity sprung first in the media, the refusal to fully share alleged evidence against them, the refusal to follow the international standards of fairness and procedural justice to allow them to reply to their critics, lack of institutional legal support, and, most astonishingly and chillingly of all, the recruitment, according to this article, of three psychiatrists to question the state of mind of one of these editors.

Now, I am not a historian of psychiatry, but the use of psychiatry as a tool against dissent, the attempts to pervert psychiatric practice, enforce psychiatric evaluation and treatment recalls the abuses of some very recent totalitarian regimes. The use of psychiatry to label political opponents as paranoid, or schizophrenic or suffering from personality disorders or unexplainable suspicious behaviours. Psychiatry is a means to control people, pressure people, eliminating critics from the public sphere.

To those of us watching outside Croatia, who love your country, who are committed in what they publish to the values of your country, this turn of events is unbelievable, is extraordinary. It is actually tragic for Croatian society and scholarly community, because, let me be very clear about this, in your editors of the *Croatian Medical Journal* you have real intellectual leaders. Clinical trial registration was first born in an International Committee of Medical Journal Editors meeting that took place here in Croatia. This is a foundation stone for unbiased knowledge and research integrity. One of the authors there – it is Prof Ana Marušić. A sequence of publications has followed on clinical trial registration, where Prof Marušić, one of the editors of the *Croatian Medical Journal*, is one of the intellectual leaders of this movement in science for research integrity. And a third editorial was again co-signed by Prof Marušić. Prof Marušić has been a Past President of the World Association of Medical Editors, the only truly global organization of medical editors that exists. She is currently president of the Council of Science Editors, the most distinguished editorial organization in the world today. She is the president of that organization, she is a leader of editors in the world, and yet what has she gone through? Her leadership illustrates the pride that Croatia can and should feel about the reputation of your journal and its editors and I must tell you the incredible damage to that reputation that has taken place in the way this present dispute has been conducted.

I have followed the debate around the *Croatian Medical Journal* carefully from abroad and this debate seems to me to be

emblematic of a larger struggle that has taken place on Croatia, across the nation, the political struggle for a great and respected European nation in transition. The country that under the current government has committed itself bravely and, in my view admirably, astonishingly actually, to a society dedicated to knowledge and education and research as a means towards stable and sustainable economic and democratic growth. That is a lesson that I have been free to invite your minister to write about in *The Lancet*, because it is a lesson that I want everybody in the world to hear because it is truly remarkable. But what is challenging, and understandably so, is that a commitment to knowledge and scholarship demands a parallel commitment, and this is tough, even not just a commitment but encouraging – dissent. Tolerance of dissent is a hallmark of a strong democracy because dissent provides the kinetic energy behind social transformation through scholarly inquiry. Editors, let's face it, are minor players in the theatre of democracy. We are just curators of the scientific record. Ninety nine percent of the time we are invisible and we are silent and we should allow the scientists to rightly occupy the public stage, but one percent of the time, just one percent of the time, editors have to speak. They have to act quickly; they have to act decisively when something goes wrong. They have to step forward and have to defend their community when a transgression takes place. And that is an uncomfortable place to be, but it is a necessary place for editors to occupy. The place of science in society has not always been guaranteed. John Ruskin wrote "The use of word *scientia* (science) as if it differed from knowledge is a modern barbarism, enhanced usually by the assumption that the knowledge of the difference between acids and alkalis is a more respectable one than that of the difference between vice and virtue." – he wrote. Science is not entirely about acids and alkalis; it is not only about interesting experiments and reliable facts. Science is also about vice and virtue and the way that the academy responds to vice and virtue reflects the moral state of our wider community. Croatia has many friends across Europe and North America and I count myself as a friend to your country. Please, I beg you; let us work harder to strengthen those ties of friendship, through respect, trough integrity, and through a shared European vision of what we can achieve together. Thank you very much.

International publications of authors from Bosnia and Herzegovina in Current Contents indexed publications in 2007

1. Simunovic VJ, Hren D, Ivanis A, Dørup J, Krivokuca Z, Ristic S, Verhaaren H, Sonntag HG, Ribaric S, Tomic S, Vojnikovic B, Seleskovic H, Dahl M, Marusic A, Marusic M. Survey of attitudes towards curriculum reforms among medical teachers in different socio-economic and cultural environments. Med Teach. 2007;29(8): 33-5.

Mostar University School of Medicine, Bosnia and Herzegovina.

BACKGROUND: Curriculum reforms in medical schools require cultural and conceptual changes from the faculty. AIMS AND METHODS: We assessed attitudes towards curriculum reforms in different academic, economic, and social environments among 776 teachers from 2 Western European medical schools (Belgium and Denmark) and 7 medical schools in 3 countries in post-communist transition (Croatia, Slovenia, Bosnia and Herzegovina). The survey included a 5-point Likert-type scale on attitudes towards reforms in general and towards reforms of medical curriculum (10 items each). RESULTS: Teaching staff from medical schools in Bosnia and Herzegovina had a more positive attitude towards reforms of medical curriculum (mean score 36.8 out of maximum 50 [95% CI 36.1 to 37.3]) than those from medical schools in Croatia or Slovenia (30.7 [29.8 to 31.6]) or Western Europe (27.7 [27.1 to 28.3]) ($P < 0.001$, ANOVA). Significant predictors of positive attitudes towards medical curriculum reform in post-communist transition countries, but not in Western European schools, was younger age, as well as female gender in Bosnia and Herzegovina. CONCLUSIONS: Factors influencing faculty attitudes may not be easy to identify and may be specific for different settings. Their identification and management is necessary for producing sustainable curriculum reform.

2. Brekalo Z, Kvesić A, Galić G, Kukić-Brusić S, Martinović V, Jonovska S. Burkitt's lymphoma in the boy: infiltration in the stomach, colon and the retroperitoneum–ileocecal invagination. Coll Antropol. 2007;31(4):1183-6.

Clinic of Surgery and Urology, University Hospital, Mostar, Bosnia and Herzegovina.

A 4-year-old boy was hospitalised because showing signs of weakness, slight pain in the abdomen and while urinating. The symptoms occurred 7 days before hospitalisation. The boy did not vomit, nor did he have the urge to vomit, the defecation was regular showing no traces of blood. The physical visit a soft and painless tumefaction was confirmed ileocecally. The echography tests and the computed tomography suggested invagination, not excluding the second substrate. Barium enema showed irreductible invagination. The operative test showed that it was about the ileocolic invagination with extreme thickening of the cecum, the ascedental colon, the intestine and the retroperitoneum walls. A resection of the small intestine and a ileocolic anastomosis was performed. The pathohistological test shows the primar abdominal Burkitt's lymphoma. In spite of the subsequent therapy the boy dies three weeks after the first symptoms' manifestation. We, herewith, suggest at the importance of the echography analysis when diagnosing the Burkitt's tumor and give advantage to this analysis against the computerized tomography. We also point at the huge level of malignancy of the Burkitt's tumor in this boy.

3. Uzunović-Kamberović S, Zorman T, Heyndrickx M, Smole Mozina S. Role of poultry meat in sporadic Campylobacter infections in Bosnia and Herzegovina: laboratory-based study. Croat Med J. 2007;48(6):842-51.

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AIM: To investigate genetic diversity and specificity of Campylobacter jejuni and Campylobacter coli strains isolated from humans, retail poultry meat, and live farm chickens in Zenica-Doboj Canton, Bosnia and Herzegovina, and identify the role of poultry meat in sporadic Campylobacter infections. METHODS: We determined the type of Campylobacter species using standard microbiological methods and multiplex polymerase chain reaction (PCR), and performed pulsed field gel-electrophoresis (PFGE) and restriction fragment length polymorphism (RFLP) typing of the flaA gene to investigate genetic diversity among the isolates. RESULTS: We isolated C jejuni and C coli from 75 (5.2%) of 1453 samples of consecutive outpatients with sporadic diarrhea; from 51 (34.7%) of 147 samples of poultry meat; and from 15 out of 23 farm chicken samples. The proportion of C coli found among human (30.1%), poultry meat (56.9%), and farm chicken isolates (53.3%), was greater than the proportion of C jejuni. Fourteen and 24 PFGE genotypes were identified among 20 C coli and 37 C jejuni isolates, respectively. Identical PFGE genotypes were found in two cases of human and poultry meat isolates and two cases of poultry meat and farm chicken isolates. CONCLUSION: Only a minority of human Campylobacter isolates shared identical PFGE type with poultry meat isolates. Although poultry is the source of a certain number of human infections, there may be other more important sources. Further research is required to identify the environmental reservoir of Campylobacter spp responsible for causing human disease and the reason for the high prevalence of C coli human infections in this region.

4. Tahirovic H, Toromanovic A, Bacaj D, Hasanovic E. Ketoacidosis at onset of type 1 diabetes mellitus in children in Bosnia and Herzegovina: frequency and clinical presentation. J Pediatr Endocrinol Metab. 2007;20(10):1137-40.

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5. Redzić SS. The ecological aspect of ethnobotany and ethnopharmacology of population in Bosnia and Herzegovina. Coll Antropol. 2007;31(3): 869-90.

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This paper contains first systematical revision of the results on traditional use of wild medicinal and aromatic herbs on the territory of Bosnia and Herzegovina (B&H)--west of Balkan Peninsula; Southeast of Europe. There have been detected 227 plants belonging to 71 different plant families, which are being used with ethno therapeutic purpose. Results were obtained by method of open ethno botanical interview which comprised 150 persons, whose average age was 63. Medicinal plants in ethno therapy are being used either in fresh, raw or dried condition. Different herbal parts, depending on period of vegetation season, sometimes even in winter, are basis for preparation of infusions (59%), decoct (19%), tinctures (4%). Especially original are balms known as Bosnian "mehlems", which are fresh cuted herbal parts mixed with lukewarm resin, raw cow butter or honey. In ethno therapy are mostly being used aerial plant organs. Majority of herbs is being used for treatment of illnesses of respiratory (22%), gastrointestinal (19%) and urinary and genital system (9%), for treatment of skin conditions (11%), as well as for nervous system and heart diseases (16%). The most original plants on the field of ethno pharmacology, comparing with ethno therapy practice of other regions, are as follows: Ballota nigra, Aesculus hippocastanum, Calluna vulgaris, Centaurea cyanus, Euphrasia rostkoviana, Geranium robertianum, Gentiana asclepiadea, Helichrysum italicum, Lycopodium clavatum, Marrubium vulgare, Nepeta cataria, Populus tremula, Ruta graveolens, Tamus communis, Teucrium montanum, T. chamaedrys, and endemic plants Gentiana lutea subsp. symphyandra, Teucrium arduini, Micromeria thymifolia, Satureja montana, S. subspicata, Rhamnus fallax and Viola elegantula. There haven't been noticed significant differences in the frequencies of medicinal plants use among different ethnical groups. But, it has been perceived that longer ethno therapeutic tradition possess inhabitants of sub- and Mediterranean areas, as well as inhabitants of the mountain areas of B&H, regardless their ethnicity.

6. Tahirovic I, Sofic E, Sapcanin A, Gavrankapetanovic I, Bach-Rojecky L, Salkovic-Petrisic M, Lackovic Z, Hoyer S, Riederer P.Brain antioxidant capacity in rat models of betacytotoxic-

induced experimental sporadic Alzheimer's disease and diabetes mellitus. J Neural Transm Suppl. 2007; (72):235-40.

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It is believed that oxidative stress plays a central role in the pathogenesis of metabolic diseases like diabetes mellitus (DM) and its complications (like peripheral neuropathy) as well as in neurodegenerative disorders like sporadic Alzheimer's disease (sAD). Representative experimental models of these diseases are streptozotocin (STZ)-induced diabetic rats and STZ-intracerebroventricularly (STZ-icv) treated rats, in which antioxidant capacity against peroxyl (ORAC(-ROO)*) and hydroxyl (ORAC(-OH)*) free radical was measured in three different brain regions (hippocampus, cerebellum, and brain stem) by means of oxygen radical absorbance capacity (ORAC) assay. In the brain of both STZ-induced diabetic and STZ-icv treated rats decreased antioxidant capacity has been found demonstrating regionally specific distribution. In the diabetic rats these abnormalities were not associated with the development of peripheral diabetic neuropathy. Also, these abnormalities were not prevented by the icv pretreatment of glucose transport inhibitor 5-thio-D-glucose in the STZ-icv treated rats, suggesting different mechanism for STZ-induced central effects from those at the periphery. Similarities in the oxidative stress alterations in the brain of STZ-icv rats and humans with sAD could be useful in the search for new drugs in the treatment of sAD that have antioxidant activity.

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7. Pranjić N, Brković A, Beganlić A.Discontent with financial situation, self-rated health, and well-being of adolescents in Bosnia and Herzegovina: cross-sectional study in Tuzla Canton. Croat Med J. 2007;48(5):691-700.

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AIM: To examine the relationship between quality of life, self-rated health, and well-being and to establish the relationship between discontent with familial financial situation and health in adolescents living in the Tuzla Canton. METHOD: The study comprised a random sample of 356 high school students aged 16, coming from 15 different classes of 16 high schools in the Tuzla municipality. Data were obtained using a validated self-reporting questionnaire on demographic and socioeconomic background, structure, and dynamics of the adolescent's family, life-style, perception, and satisfaction with the financial situation and current health status, as well as social relationships and health care provided in school settings. RESULTS: In 11% (n=40) of students' households several poverty indicators were present. Twenty three percent (n=82) of the examinees were dissatisfied with the financial situation in their families, and 73% of them came from local, non-refugee families. They presented with progressive symptoms of unhappiness and expressed discontent with their health condition, and even self-hate in comparison with adolescents who were satisfied with the financial situation in their families (chi(2)=21.5; P=0.001). The prevalence of self-rated mental symptoms was significantly lower among adolescents who were satisfied with their financial situation than in those who were dissatisfied (symptoms of depression 57/274 vs 40/82, P=0.001; sadness 73/274 vs 45/82, P=0.001; moroseness 34/274 vs 19/82, P=0.001; under-sedation 29/274 vs 18/82, P=0.001; bad marks and school failures 31/274 vs 20/82, P=0.001; suicidal attempts 11/274 vs 7/82, P=0.001, respectively). Using linear regression analysis we found that adolescents' satisfaction with the financial situation was a major factor predicting depression (OR, 1.57; 95% CI, 1.158-1.855), loss of appetite (OR, 0.82; 95% CI, 0.561-1.235), distraction (OR, 1.19; 95% CI, 0.837-1.154), unhappiness (OR, 1.05; 95% CI, 0.686-1.405), and inability to perform at school as expected (OR, 1.24; 95% CI, 0.903-1.581). CONCLUSION: Discontent with the financial situation significantly reduces the quality of mental health, leads to inappropriate patterns of behavior, and endangers future perspectives and well-being of adolescents.

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8. Zaciragic A, Lepara O, Valjevac A, Arslanagic S, Fajkic A, Hadzovic-Dzuvo A, Avdagic N, Alajbegovic A, Mehmedika-Suljic E, Coric G. Elevated serum C-reactive protein concentration in Bosnian patients with probable Alzheimer's disease. J Alzheimers Dis. 2007;12(2):151-6.

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Studies indicate that inflammatory mechanisms may play an important role in the pathogenesis of Alzheimer's disease (AD). C-reactive protein (CRP), marker and mediator of inflammation, has been detected in lesions typical for the affected areas of AD brain. There have been conflicting reports on serum CRP concentration in AD. Scarce data exist on association of CRP and measures of adiposity in AD patients. Thus, we investigated serum CRP concentration in fifteen overweight institutionalized patients with probable AD and fifteen age-matched control subjects. Body mass index (BMI) and waist/hip ratio (WHR) were calculated for

each subject included in the study. Age, systolic and diastolic blood pressure, BMI and WHR did not differ significantly between the two groups. Serum CRP concentration was significantly higher in patients with AD compared to controls (p<0.0001). Although not significant, positive correlations between serum levels of CRP and BMI and WHR were found. Obtained results support the notion that low-grade inflammation is present in patients with AD. Absence of significant association between CRP and measures of total and central adiposity in overweight AD patients needs further investigation and explanation.

9. Redzić A, Hadzihalilović J. Influence of some socio-economic factors on growth and development of the boys in the Tuzla region (Bosnia and Herzegovina). Coll Antropol. 2007;31(2):427-34.

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The impact of certain exogenous factor (socio-economic, ecological) has been investigated with special attention paid to the parents' living standard, and number of family members on some anthropometric parameters like: body height, body mass, chest circumference, upper leg circumference, upper arm circumference, sitting height, arm length, leg length, pelvis width, shoulders width, lenght of head and with of head on the sample of 698 boys aged 11 to 16 (17) years in the Tuzla region (the northeastern Bosnia, Western Balkan peninsula). Anthropometric measurements have been carried out using methodology proposed by the International Biological program (IBP). The results of these investigations have shown that there is a certain impact of the socio-economic conditions on the growth and development of boys. Children from families that have better living standard are, as a rule, taller, which is indicated by the statistical significant differences (P > 0.01). This trend indicates also value of Body Mass Index (BMI), which is in younger children from the families with lower living standard 16, while in the same category in the children from the families with better living standard it has value 18.5. The real impact of living conditions on the dynamics of development could be the best seen in the period of puberty. The number of children in the family has negative relationship with anthropometric features. Statistically significant differences (P > 0.001) have been detected in numerous analysed features in families with one or two children in comparison with families with three, four, or five children. Therefore, BMI has been significantly lower (16) in children from families with several children, while in the families with one child in the same growth class (11 years) it was significantly higher (17.4). Similar value of BMI (17.9) have children from the families with five children and which are 17 years old. Besides socio-economic conditions, high level of environmental pollution which is typical for Tuzla region for a long time, has also significant impact on the growth and development of children.

10. Klupka-Sarić I, Ristić S, Sepcić J, Kapović M, Peterlin B, Materljan E, Jurisić T, Mamić DM, Burina A, Sulentić V. Epidemiology of multiple sclerosis in western Herzegovina. Clin Neurol Neurosurg. 2007;109 (9):779-83.

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OBJECTIVES: To determine epidemiological rates of multiple sclerosis (MS) in western Herzegovina. PATIENTS AND METHODS: We analysed data from 81 MS patients (49 females, 32 males) on the prevalence day, 31 December 2003. Patient information was obtained from a search of all available medical records from the period 1994-2003 in the investigated area. RESULTS: Crude prevalence of MS was 27/100,000 (95% confidence interval (CI) 20-34). Prevalence was highest in the mountainous municipality of Posusje (56/100,000) and lowest in the coastal municipality of Neum (0 incidence). The annual incidence of MS was 1.6/100,000 (95% CI 0-3.3). The female/male ratio of MS was 1.5. The mean age of the patients on prevalence day was 40.0+/-11.6 years, and the mean age at disease onset was 31.0+/-7.1 years. Eight (10%) of the patients had a first-degree relative with MS. The primary progressive (PP) disease course was observed only in females. Visual symptoms were the initial symptom of MS in 6 (7%) of the patients. CONCLUSIONS: Western Herzegovina is an area of moderate risk for MS, and the distribution of MS in western Herzegovina is heterogeneous. PP-MS occurred only in females, and involvement of the visual pathways as the initial symptom of MS was low.

11. Zerem E, Hadzic A. Sonographically guided percutaneous catheter drainage versus needle aspiration in the management of pyogenic liver abscess. AJR Am J Roentgenol. 2007;189(3):W138-42.

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OBJECTIVE: The purpose of this study was to determine the effectiveness of percutaneous catheter drainage (PCD) and to compare PCD with percutaneous needle aspiration in the management of liver abscess. SUBJECTS AND METHODS: Sixty patients with pyogenic liver abscess were randomly assigned to two groups in a prospective study. Antibiotics were

administered for 10 days, starting the day of the beginning of percutaneous treatment. One group was treated with sonographically guided PCD and the other group with repeated percutaneous needle aspiration. Percutaneous needle aspiration was attempted a maximum of three times. Lack of response to the third aspiration was considered failure of treatment; these patients were treated with PCD but were not included in the PCD group for analysis. Patient demographics, duration of hospital stay, treatment outcome, and complications were analyzed. RESULTS: Percutaneous needle aspiration was successful in 20 (67%) of the 30 patients after one (n = 12), two (n = 7), or three (n = 1) aspirations. PCD was curative in all 30 patients after one (n = 24) or two (n = 6) procedures. All abscesses 50 mm or less in longest diameter were successfully managed, 10 by percutaneous needle aspiration and 12 by PCD. None of patients in the percutaneous needle aspiration group with multiloculated abscesses (n = 5) was successfully treated. Hospital stay did not differ significantly between the groups. There were no complications related to the procedure. CONCLUSION: PCD is more effective than percutaneous needle aspiration in the management of liver abscess. Percutaneous needle aspiration can be used as a valid alternative for simple abscesses 50 mm in diameter or smaller.

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12. Marjanović D, Durmić-Pasić A, Bakal N, Haverić S, Kalamujić B, Kovacević L, Ramić J, Pojskić N, Skaro V, Projić P, Bajrović K, Hadziselimović R, Drobnic K, Huffine E, Davoren J, Primorac D. DNA identification of skeletal remains from the World War II mass graves uncovered in Slovenia. Croat Med J. 2007;48(4):513-9.

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AIM: To present the joint effort of three institutions in the identification of human remains from the World War II found in two mass graves in the area of Skofja Loka, Slovenia. METHODS: The remains of 27 individuals were found in two small and closely located mass graves. The DNA was isolated from bone and teeth samples using either standard phenol/chloroform alcohol extraction or optimized Qiagen DNA extraction procedure. Some recovered samples required the employment of additional DNA purification methods, such as N-buthanol treatment. Quantifiler Human DNA Quantification Kit was used for DNA quantification. PowerPlex 16 kit was used to simultaneously amplify 15 short tandem repeat (STR) loci. Matching probabilities were estimated using the DNA View program. RESULTS: Out of all processed samples, 15 remains were fully profiled at all 15 STR loci. The other 12 profiles were partial. The least successful profile included 13 loci. Also, 69 referent samples (buccal swabs) from potential living relatives were collected and profiled. Comparison of victims' profile against referent samples database resulted in 4 strong matches. In addition, 5 other profiles were matched to certain referent samples with lower probability. CONCLUSION: Our results show that more than 6 decades after the end of the World War II, DNA analysis may significantly contribute to the identification of the remains from that period. Additional analysis of Y-STRs and mitochondrial DNA (mtDNA) markers will be performed in the second phase of the identification project.

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13. Huel RL, Basić L, Madacki-Todorović K, Smajlović L, Eminović I, Berbić I, Milos A, Parsons TJ. Variant alleles, triallelic patterns, and point mutations observed in nuclear short tandem repeat typing of populations in Bosnia and Serbia. Croat Med J. 2007;48(4):494-502.

International Commission on Missing Persons, Sarajevo, Bosnia and Herzegovina.

AIM: To present a compendium of off-ladder alleles and other genotyping irregularities relating to rare/unexpected population genetic variation, observed in a large short tandem repeat (STR) database from Bosnia and Serbia. METHODS: DNA was extracted from blood stain cards relating to reference samples from a population of 32800 individuals from Bosnia and Serbia, and typed using Promega's PowerPlex16 STR kit. RESULTS: There were 31 distinct off-ladder alleles were observed in 10 of the 15 STR loci amplified from the PowerPlex16 STR kit. Of these 31, 3 have not been previously reported. Furthermore, 16 instances of triallelic patterns were observed in 9 of the 15 loci. Primer binding site mismatches that affected amplification were observed in two loci, D5S818 and D8S1179. CONCLUSION: Instances of deviations from manufacturer's allelic ladders should be expected and caution taken to properly designate the correct alleles in large DNA databases. Particular care should be taken in kinship matching or paternity cases as incorrect designation of any of these deviations from allelic ladders could lead to false exclusions.

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14. Milos A, Selmanović A, Smajlović L, Huel RL, Katzmarzyk C, Rizvić A, Parsons TJ. Success rates of nuclear short tandem repeat typing from different skeletal elements. Croat Med J. 2007;48(4):486-93.

International Commission on Missing Persons, Sarajevo, Bosnia and Herzegovina.

AIM: To evaluate trends in DNA typing success rates of different skeletal elements from mass graves originating from conflicts that occurred in the former Yugoslavia (Bosnia and Herzegovina and Kosovo) during the 1990s, and to establish correlation between skeletal sample age and success of high throughput short tandem repeat (STR) typing in the large data set of the International Commission on Missing Persons. METHOD: DNA extraction and short tandem repeat (STR) typing have been attempted on over 25000 skeletal samples. The skeletal samples originated from different geographical locations where the conflicts occurred and from different time periods from 1992 to 1999. DNA preservation in these samples was highly variable, but was often significantly degraded and of limited quantity. For the purpose of this study, processed samples were categorized according to skeletal sample type, sample age since death, and success rates tabulated. RESULTS: Well-defined general trends in success rates of DNA analyses were observed with respect to the type of bone tested and sample age. The highest success rates were observed with samples from dense cortical bone of weight-bearing leg bones (femur 86.9%), whereas long bones of the arms showed significantly lower success (humerus 46.2%, radius 24.5%, ulna 22.8%). Intact teeth also exhibited high success rates (teeth 82.7%). DNA isolation from other skeletal elements differed considerably in success, making bone sample selection an important factor influencing success. CONCLUSION: The success of DNA typing is related to the type of skeletal sample. By carefully evaluating skeletal material available for forensic DNA testing with regard to sample age and type of skeletal element available, it is possible to increase the success and efficiency of forensic DNA testing.

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15. Davoren J, Vanek D, Konjhodzić R, Crews J, Huffine E, Parsons TJ. Highly effective DNA extraction method for nuclear short tandem repeat testing of skeletal remains from mass graves. Croat Med J. 2007;48(4):478-85.

International Commission on Missing Persons, Sarajevo, Bosnia and Herzegovina.

AIM: To quantitatively compare a silica extraction method with a commonly used phenol/chloroform extraction method for DNA analysis of specimens exhumed from mass graves. METHODS: DNA was extracted from twenty randomly chosen femur samples, using the International Commission on Missing Persons (ICMP) silica method, based on Qiagen Blood Maxi Kit, and compared with the DNA extracted by the standard phenol/chloroform-based method. The efficacy of extraction methods was compared by real time polymerase chain reaction (PCR) to measure DNA quantity and the presence of inhibitors and by amplification with the PowerPlex 16 (PP16) multiplex nuclear short tandem repeat (STR) kit. RESULTS: DNA quantification results showed that the silica-based method extracted on average 1.94 ng of DNA per gram of bone (range 0.25-9.58 ng/g), compared with only 0.68 ng/g by the organic method extracted (range 0.0016-4.4880 ng/g). Inhibition tests showed that there were on average significantly lower levels of PCR inhibitors in DNA isolated by the organic method. When amplified with PP16, all samples extracted by silica-based method produced 16 full loci profiles, while only 75% of the DNA extracts obtained by organic technique amplified 16 loci profiles. CONCLUSIONS: The silica-based extraction method showed better results in nuclear STR typing from degraded bone samples than a commonly used phenol/chloroform method.

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16. Zukanović A, Kobaslija S, Ganibegović M. Caries risk assessment in Bosnian children using Cariogram computer model. Int Dent J. 2007;57(3):177-83.

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AIM: To examine caries risk using the Cariogram model, interactive PC program for caries risk evaluation in 12-year-old children and to correlate caries risk in children of different socioeconomic backgrounds. MATERIAL AND METHODS: 109, Sarajevo 12-year-olds in three groups based on socioeconomic background. Baseline data on general health condition, diet frequency and use of fluoride were obtained. DMFT and plaque scores were calculated. Saliva analyses included lactobacillus and mutans streptococci levels in saliva, saliva secretion and buffer capacity. Scores were entered into the Cariogram model and risk was calculated for each child. RESULTS: Most 12-year-old children have a medium risk of caries, with a 59.4% chance of avoiding future caries. In an average caries risk profile of children from Sarajevo the dominant sector is diet, with 12.5% risk; bacteria sector (plaque and mutans streptococci level) 10.8% risk; susceptibility (fluoride, saliva secretion and buffering capacity) 9.7% risk; circumstances (caries experience and medical history) 7.4% risk. Caries risk profiles showed that there are differences in the socioeconomic status of children with significantly greater risk in children with poor living conditions who also have the most unfavourable caries risk profiles. CONCLUSIONS: The Cariogram model can successfully determine caries risk profiles for 12-year-old children of different socioeconomic status and can be used in developing preventive strategies for reducing caries risk in children.

17. Vranić S, Bilalović N, Lee LM, Kruslin B, Lilleberg SL, Gatalica Z. PIK3CA and PTEN mutations in adenoid cystic carcinoma of the breast metastatic to kidney. Hum Pathol. 2007;38(9):1425-31.

Department of Pathology, Clinical Center of University of Sarajevo, Sarajevo 71000, Bosnia and Herzegovina.

Adenoid cystic carcinoma (ACC) of the breast rarely metastasizes and has been associated with excellent prognosis. We describe a patient with renal metastasis of primary breast ACC 5 years after the mastectomy. A detailed molecular genetic analysis of the primary and metastatic tumors demonstrated somatic mutations in 2 well-known cancer genes associated with regulation of PI3K/AKT signaling pathway: (1) PIK3CA, which encodes the catalytic alpha subunit of the phosphoinositide-3-kinase, and (2) PTEN, which encodes phosphatase and tensin homolog. The mutation identified in PIK3CA (Ex1+169 A>C) predicts an amino acid change from isoleucine to methionine at codon 31 (I31M) and resides in the p85-binding domain of exon 1. The mutation identified in PTEN (IVS4-3 C>T) resides in intron 4 near the splice acceptor site of exon 5 and was associated with an aberrant PTEN transcript lacking exon 5, which is necessary for protein tyrosine phosphatase function and tumor suppressor properties of PTEN. Increased promoter methylation of PTEN was present in renal metastasis, coinciding with the decrease in the level of normal PTEN transcript. These coexistent mutations/epigenetic inactivations in PI3K/AKT pathway may be responsible for the unusually aggressive course of ACC.

18. Tahirovic I, Sofic E, Sapcanin A, Gavrankapetanovic I, Bach-Rojecky L, Salkovic-Petrisic M, Lackovic Z, Hoyer S, Riederer P. Reduced brain antioxidant capacity in rat models of betacytotoxic-induced experimental sporadic Alzheimer's disease and diabetes mellitus. Neurochem Res. 2007;32(10):1709-17.

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It is believed that oxidative stress (OS) plays a central role in the pathogenesis of metabolic diseases like diabetes mellitus (DM) and its complications (like peripheral neuropathy) as well as in neurodegenerative disorders like sporadic Alzheimer's disease (sAD). Representative experimental models of these diseases are streptozotocin (STZ)-induced diabetic rats and STZ-intracerebroventricularly (STZ-icv) treated rats, in which antioxidant capacity (AC) against peroxyl (ORAC(-ROO) (*)) and hydroxyl (ORAC(-OH) (*)) free radicals (FR) was measured in three different brain regions: the hippocampus (HPC), the cerebellum (CB), and the brain stem (BS) by means of oxygen radical absorbance capacity (ORAC) assay. In the brain of both STZ-induced diabetic and STZ-icv treated rats decreased AC has been found demonstrating regionally specific distribution. In the diabetic rats these abnormalities were not associated with the development of peripheral diabetic neuropathy (PDN). Also, these abnormalities were not prevented by the intracerebroventricularly (icv) pretreatment of glucose transport inhibitor 5-thio-D: -glucose (TG) in the STZ-icv treated rats, suggesting different mechanism of STZ-induced central effects from those at the periphery. Similarities of the OS alterations in the brain of STZ-icv rats and humans with sAD could be useful in the search for the new drugs in the treatment of sAD that have antioxidant activity. In the STZ-induced diabetic animals the existence of PDN was tested by the paw pressure test, 3 weeks following the diabetes induction. Mechanical nociceptive thresholds were measured three times at 10-min intervals by applying increased pressure to the hind paw until the paw-withdrawal or overt struggling was elicited. Only those diabetic animals which demonstrated decreased withdrawal threshold values in comparison with the control non-diabetic animals (C) were considered to have developed the PDN.

19. Brekalo Z, Kvesić A, Nikolić H, Tomić D, Martinović V. Snodgrass' urethroplasty in hypospadias surgery in Clinical Hospital Mostar-preliminary report. Coll Antropol. 2007;31(1):189-93.

Department of Pediatric Surgery, Clinic of Surgery nad Urology, Clinical Hospital, Mostar, Bosnia and Herzegovina.

Amongst the various methods of reconstructing the hypospadic urethra such as the MAGPI, Mathieu's and Preputial island flap urethroplasty method and the Snodgrass method, the latter is being used more frequently nowadays in patients with the urethral meatus located in the proximity of the penis. In the Pediatric ward at Mostar Clinical Hospital, we have recently adopted the Snodgrass method when reconstructing the hypospadic urethra. We herewith present our research regarding the successful results in adopting the aforementioned method. Success was evaluated according to the frequency of post-operative complications, as well as the patients' satisfaction with the functional and the cosmetic result of the urethra reconstruction. The conclusions relating to our research result in an addition basis from which to evaluate whether the Snodgrass method should receive privileged preference in future operative treatment of the hypospadias over others methods, as can be seen from our research.

20. Uzunovic-Kamberovic S, Bedenic B, Vranes J. Predominance of SHV-5 beta-lactamase in enteric bacteria causing community-acquired urinary tract infections in Bosnia and Herzegovina. Clin Microbiol Infect. 2007;13(8):820-3.

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The beta-lactamases produced by 14 non-duplicate Klebsiella pneumoniae isolates and five Escherichia coli isolates from urine samples obtained from outpatients were characterised by isoelectric focusing, substrate profile determination, PCR and sequencing of bla(SHV) genes. Three E. coli A15 R(+) transconjugants were identified as isolates that produced SHV-5 beta-lactamase. This report is the first description of SHV-5 beta-lactamase among community isolates. Since the isolates showed distinct pulsed-field gel electrophoresis patterns, it was concluded that there was no clonal spread of bla(TEM) and bla(SHV) genes, and that dissemination of the bla(TEM) and bla(SHV) genes was the result of exchange of plasmids among different clones.

21. Ibrulj S, Rahmanovic A, Haveric S, Haveric A, Pasic AD. Cytogenetic evaluation of paracetamol effects in human lymphocytes culture. Drug Chem Toxicol. 2007;30(2):133-43.

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Paracetamol is a common analgesic and antipyretic drug. It has been recognized as one of the most ordinary medications taken in overdoses. We examined the possible genotoxic effects of high paracetamol concentrations expected to occur after overdose. Paracetamol was added to the cultures at the beginning of the cultivation period. Separate cultures for three tested concentrations of paracetamol (50 microg/mL, 100 microg/mL, and 200 microg/mL) were set. Effects of paracetamol were evaluated by micronucleus cytokinesis-block assay, chromosome aberration analysis, and nuclear division index. Results demonstrate that paracetamol concentration of 200 microg/mL expresses certain genotoxic effects in human peripheral blood lymphocytes.

22. Pilav A. A view from Bosnia and Herzegovina. Interview by Emma Wilkinson. Circulation. 2007; 24;115(16):f73-4.

23. Rifatbegović M, Assunção P, Poveda JB, Pasić S. Isolation of Mycoplasma bovis from the respiratory tract of cattle in Bosnia and Herzegovina. Vet Rec. 2007;160(14):484-5.

Department of Microbiology and Infectious Diseases, Veterinary Faculty, University of Sarajevo, Zmaja od Bosne 90, 71000 Sarajevo, Bosnia and Herzegovina.

24. Brkić F, Umihanić S. Tracheobronchial foreign bodies in children. Experience at ORL clinic Tuzla, 1954-2004. Int J Pediatr Otorhinolaryngol. 2007;71(6):909-15.

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OBJECTIVE: To determine the clinical characteristics and the results of bronchoscopic treatment of children due to foreign body aspiration in a university hospital. SETTING: Department of Otorhinolaryngology and Maxillofacial Surgery, University Clinical Center Tuzla, Bosnia and Hercegovina. METHOD: The analysis of the cases of aspirated foreign bodies within the period from January 1954 to December 2004. The analyzed patients were the children up to 14 years of age. All cases underwent the bronchoscopy. Each patient was analyzed for age, sex, nature and location of the foreign body, results of bronchoscopic removal, complications of bronchoscopy and presence of foreign bodies in the airways. RESULTS: Six hundred and sixty-two children who underwent bronchoscopy for removal of foreign body in the airways were evaluated. From evaluated children 66.8% were boys, ages ranging from 9 months to 14 years. Foreign bodies were more frequent in children under 3 years of age (65.2%). Most of the foreign bodies removed were organic (87.1%) and more frequently found in the right bronchial tree (53%). CONCLUSIONS: More attention is necessary to the prevention of aspirations. Prevention of aspiration of foreign bodies is better than cure. Public awareness through mass media needs attention to prevent foreign body inhalation.

25. Tahirovic H, Imsiragic-Zovko S, Toromanovic A, Begic L. Assessment of the success of implementation of new rule book on salt iodination in Federation of Bosnia and Herzegovina. J Endocrinol Invest. 2007;30(1):9-12.

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The aim of this study was to determine the success of an increase in the level of salt iodization which was

increased to 20-30 mg iodine per kilo of salt, 2 yr after the introduction of the new mandatory salt iodination. This prospective study was performed at level of Federation of Bosnia and Herzegovina (FBH). We singled out 60 cluster school-based surveys (6 cluster surveys in each canton) with equal representation of urban and rural areas. Within each cluster, between 10 to 30 subjects (both males and females) aged 11, 12, 13 and 14 were randomly selected. The study included a total of 962 schoolchildren. The mean iodine level per 1 kg of salt for whole FBH was 21.4+/-5.2. It ranged from 2.1 to 41.3 mg/kg. A significant improvement in urinary iodine excretion medians was detected in the current survey in all cantons and on the entire territory of FBH, compared to results from a previous study conducted in 1999. The urinary iodine excretion in schoolchildren in the whole FBH varied from 50.6 to 303.8 mug/l with a median of 139.5 mug/l. Values of urinary iodine <100.0 mug/l were found in 15.9% of samples of schoolchildren, whereas no values <50.0 mug/l were found. In conclusion, the results of the study indicate that increased iodine supplementation of salt in 2001 was successful and that FBH is presently iodine sufficient. In the future, however, program for monitoring of iodine prophylaxis has to have two major aims: firstly, control of iodine content in salt at different levels especially at retail shops and at imported salt and secondly, iodine deficiency disorders control. Also, a periodic measurement of urinary iodine excretion needs to be planned together with the neonatal TSH screening and the establishment of a notification system for cases of hyperthyroidism.

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26. Prohic A, Ozegovic L. Malassezia species isolated from lesional and non-lesional skin in patients with pityriasis versicolor. Mycoses. 2007;50(1):58-63.

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Pityriasis versicolor (PV) is a superficial fungal infection where Malassezia species play a definite causative role, but the clinical significance of each of these species is not fully understood. The aim of our study was to analyse the prevalence of Malassezia species in PV lesions and to examine if the range of species varies with patient sex, age, direct microscopy findings and some clinical data. Ninety patients with PV completed the study. The samples were obtained by scraping the skin surface, both from lesional and non-lesional skin and then incubated on Sabouraud dextrose agar and modified Dixon agar. The yeast isolated were identified according to their macroscopic and microscoipic features and physiological characteristics. In PV lesions, the most common species was M. globosa (63%), followed by M. sympodialis (14%), M. furfur (10%), M. obtusa (8%) and M. slooffiae (4%). The most frequently isolated species from clinically healthy skin were M. globosa (49%), M. sympodialis (37%) and M. furfur (5%). We found significant difference in the distribution of Malassezia species between lesional and non-lesional skin and in the distribution of Malassezia species according to the direct microscopy findings. M. globosa in its mycelial phase is the predominant species involved in the aetiology of PV.

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27. Salkic NN, Zildzic M, Muminhodzic K, Pavlovic-Calic N, Zerem E, Ahmetagic S, Mott-Divkovic S, Alibegovic E. Intrafamilial transmission of hepatitis B in Tuzla region of Bosnia and Herzegovina. Eur J Gastroenterol Hepatol. 2007;19(2):113-8.

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OBJECTIVE: To determine (i) the prevalence of HBV infection in families of confirmed chronic carriers, (ii) possible routes of transmission and risk factors for the intrafamilial transmission, (iii) vaccination rate among family members of chronic carriers and (iv) family members with highest risk for infection. METHODS: A total of 172 family members of 67 hepatitis B surface antigen chronic carriers were tested for hepatitis B markers; 716 first-time blood donors from the same area were used as controls. RESULTS: Prevalence of hepatitis B surface antigen was higher (P<0.001) among family members of index cases (12.2%; 21/172) than among controls (3.6%; 26/716) with relative risk of 3.3 (95% confidence Intervals=1.9-5.8; P<0.05). Rate of exposure among family members was 37.8% (65/172); only 8.7% (15/172) had been vaccinated for hepatitis B virus. Difference (P<0.001) in exposure existed among family members; exposure increased with age (rhos=0.34; P<0.001). Prevalences of hepatitis B surface antigen positivity and hepatitis B virus exposure were higher among parents of index cases (P<0.005) and among offspring of female index cases (P<0.001). There were more (P<0.001) hepatitis B surface antigen-positive family members among those with mother-children relationship with index case (13/31; 41.9%) than among those with father-children (19/85; 22.4%) and horizontal (siblings and spouses) relationship (2/56; 3.6%). Significantly more (P<0.001) hepatitis B surface antigen-positive and hepatitis B virus-exposed offspring were found in families where only mother was hepatitis B surface antigen positive. Among family members of HBeAg-positive cases more hepatitis B surface antigen-positive cases and hepatitis B virus-exposed cases have been found (P<0.001). Combination of HBeAg positivity

and female sex of index case significantly increased risk for chronic carriage among family members (relative risk=24.06; 95% confidence interval=8.88-65.21; P<0.05). CONCLUSION: In the area studied, both horizontal and vertical transmission exists, but maternal route is predominant. Female sex, HBeAg positivity of index carrier and presence of hepatitis B surface antigen-positive mother inside family increased risk for hepatitis B surface antigen positivity and exposure among family members. Vaccination rate of family members of index cases is alarmingly low.

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28. Bergsland J, Kabil E, Mujanovic E, Terzic I, Røislien J, Svennevig JL, Fosse E. Training of cardiac surgeons for Bosnia and Herzegovina: outcomes in coronary bypass grafting surgery. Ann Thorac Surg. 2007;83(2):462-7.

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BACKGROUND: Bosnia and Herzegovina did not have invasive cardiac diagnosis or cardiac surgery before the recent war. With assistance from the United States and Norway, a cardiovascular clinic was developed. This study reports center-specific and surgeon-specific clinical outcomes. Since off-pump coronary bypass grafting surgery was prioritized in the treatment of coronary disease, a comparison was made between operations performed with and without cardiopulmonary bypass. METHODS: Surgeons and key staff members were trained in the United States. A Norwegian data management system for cardiac surgery was implemented and cases entered after quality review of the data. A total of 1276 patients were entered; operations were performed with cardiopulmonary bypass in 540 and without in 736. The primary surgeon was entered as a variable in an anonymous fashion. RESULTS: Overall mortality for coronary bypass grafting surgery was 1.6%, and the major complication rate was 4.5%. Patients operated on off-pump received fewer grafts and had a shorter length of stay. Unfavorable outcome was more common in patients when cardiopulmonary bypass was used in the operation. Regression analysis demonstrated that the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and use of cardiopulmonary bypass were predictors of poor outcome. The individual surgeon factor did not impact on outcomes. CONCLUSIONS: Our study confirms that coronary artery bypass grafting surgery may be performed safely in a poor country in a hospital without experience with cardiac surgery. Selection of talented staff and cooperation with international cardiac centers are crucial. Off-pump coronary artery bypass grafting surgery is suitable for a new center and does not require more training than standard procedures.

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29. Kurić L. The digital language of amino acids. Amino Acids. 2007;33(4):653-61.

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The subject of this paper is a digital approach to the investigation of the biochemical basis of genetic processes. The digital mechanism of nucleic acid and protein bio-syntheses, the evolution of biomacromolecules and, especially, the biochemical evolution of genetic language have been analyzed by the application of cybernetic methods, information theory and system theory, respectively. This paper reports the discovery of new methods for developing the new technologies in genetics. It is about the most advanced digital technology which is based on program, cybernetics and informational systems and laws. The results in the practical application of the new technology could be useful in bioinformatics, genetics, biochemistry, medicine and other natural sciences.

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30. Jelavic B, Bevanda M, Ostojic M, Leventic M, Vasilj M, Knezevic E. Tonsillar colonization is unlikely to play important role in Helicobacter pylori infection in children. Int J Pediatr Otorhinolaryngol. 2007;71(4):585-90.

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OBJECTIVE: To determine (i) seroprevalence of Helicobacter pylori (HP) infection in children undergoing tonsillectomy, (ii) possible HP colonization on tonsils of children and its importance in HP transmission, and (iii) if four examined socio-economic factors are the risk factors for HP transmission and HP colonization on tonsils in children. METHODS: Rapid urease test (RUT) of tonsils, and serologic blood tests for HP were performed in 77 children (aged 4-14 years) in Bosnia and Herzegovina (B-H), undergoing tonsillectomy. RUT positive tonsils were cultured for HP. RUT positive children were tested using (13)Carbon-urea breath test ((13)C-UBT). Information about socio-economic potential risk factors was obtained from the parents. RESULTS: Out of 139 pharyngeal and palatine tonsils, 17 palatine tonsils in 14 children were RUT positive and had negative HP culture. Eight children had positive both RUT and (13) C-UBT. There was no significant difference between children with hypertrophy and those with recurrent tonsillitis comparing their serologic tests results. There was no significant difference between seronegative (n=61) and

seropositive (n=16) children comparing their age, sex, parental education level, owning a family courtyard, attending a children's collective, and owning a pet cat. CONCLUSIONS: The results in this prospective study do not support the notion that tonsils are an important reservoir for HP transmission in children in B-H. The examined socio-economic factors did not enhance HP seropositivity rate in children.

31. Zerem E, Salkic N, Imamovic G, Terzić I. Comparison of therapeutic effectiveness of percutaneous drainage with antibiotics versus antibiotics alone in the treatment of periappendiceal abscess: is appendectomy always necessary after perforation of appendix? Surg Endosc. 2007;21(3):461-6.

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BACKGROUND: The present study was designed to compare the therapeutic effectiveness of percutaneous drainage with antibiotics versus antibiotics alone in the treatment of appendicitis complicated by periappendiceal abscess. METHODS: In a prospective study, 50 patients with acute appendicitis complicated by periappendiceal abscess > or = 3 cm in size were randomly assigned to two groups. The first group received treatment with ultrasound guided-percutaneous drainage and i.v. antibiotics (ampicillin, cefuroxime, and metronidazole), and the other group received antibiotics only. Patient's baseline characteristics, duration of hospital stay, and treatment outcome and complications were analyzed. RESULTS: Appendectomy was avoided in 16/25 patients in the drainage group and 2/25 patients in the non-drainage group during follow-up with RR of 0.39 (95% CI = 0.22-0.62; p < 0.05). One patient in the drainage group and 8 patients in the non-drainage group underwent surgery in the first month after the beginning of treatment. Eight patients in the drainage group and 15 in the non-drainage group underwent interval appendectomy. There was no statistically significant difference between the two groups regarding patient demographics, abscess size, and pretreatment clinical symptoms. Hospital stay up to the subsidence of clinical and sonographic signs was significantly shorter (p < 0.001) in the drainage group, with a mean difference of 6.4 days (95% CI = 5.0-7.9; p < 0.05). CONCLUSIONS: Percutaneous drainage with antibiotics is a safe and effective way of treating acute perforated appendicitis. The recurrence rate for these patients is relatively low, and very often interval appendectomy is not required. For patients with periappendiceal abscess > or = 3 cm in diameter, antibiotic therapy alone is insufficient and the recurrence rate is high.

32. Kapur E, Vuckovic I, Dilberovic F, Zaciragic A, Cosovic E, Divanovic KA, Mornjakovic Z, Babic M, Borgeat A, Thys DM, Hadzic A. Neurologic and histologic outcome after intraneural injections of lidocaine in canine sciatic nerves. Acta Anaesthesiol Scand. 2007;51(1):101-7.

Department of Anatomy, Medical School, University of Sarajevo, Bosnia and Herzegovina.

BACKGROUND: Inadvertent intraneural injection of local anesthetics may result in neurologic injury. We hypothesized that an intraneural injection may be associated with higher injection pressures and an increase in the risk of neurologic injury. METHODS: The study was conducted in accordance with the principles of laboratory animal care, and was approved by the Laboratory Animal Care and Use Committee. Fifteen dogs of mixed breed (16-21 kg) were studied. After general endotracheal anesthesia, the sciatic nerves (n= 30) were exposed bilaterally. Under direct vision, a 25-gauge, long-beveled needle (30 degrees) was placed either epineurally (n= 10) or intraneurally (n= 20), and 4 ml of preservative-free lidocaine 20 mg/ml was injected using an automated infusion pump (4 ml/min). Injection pressure data were acquired using an in-line manometer coupled to a computer via an analog-to-digital conversion board. After injection, the animals were awakened and subjected to serial neurologic examinations. One week later, the dogs were killed, the sciatic nerves excised and histologic examination was performed by pathologists blind to the purpose of the study. RESULTS: All perineural injections resulted in low pressures (< or = 5 psi). In contrast, eight of 20 intraneural injections resulted in high pressures (20-38 psi) at the beginning of the injection. Twelve intraneural injections, however, resulted in pressures of less than 12 psi. Neurologic function returned to baseline within 3 h after perineural injections and within 24 h after intraneural injections, when the measured injection pressures were less than 12 psi. Neurologic deficits persisted throughout the study period after all eight intraneural injections that resulted in high injection pressures. Histologic examination of the affected nerves revealed fascicular axonolysis and cellular infiltration. CONCLUSIONS: The data in our canine model of intraneural injection suggest that intraneural injections do not always lead to nerve injury. High injection pressures during intraneural injection may be indicative of intrafascicular injection and may predict the development of neurologic injury.

33. Tahirović H, Toromanović A. Incidence of type 1 diabetes mellitus in children in Tuzla Canton between 1995 and 2004. Eur J Pediatr. 2007;166(5):491-2.

Department of Pediatrics, University Clinical Center, 75000, Tuzla, Bosnia and Herzegovina. husref.tahirovic@untz.ba

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34. Mulaomerović A, Halilbasić A, Cickusić E, Zavasnik-Bergant T, Begić L, Kos J. Cystatin C as a potential marker for relapse in patients with non-Hodgkin B-cell lymphoma. Cancer Lett. 2007; 18;248(2):192-7.

Medical Faculty, University of Tuzla, Bosnia and Herzegovina.

The concentration of cysteine protease inhibitor cystatin C was determined in sera from 59 patients with non-Hodgkin B-cell lymphoma using ELISA. The sera from 43 age and sex matched healthy blood donors served as controls. Cystatin C was significantly increased in sera of patients without therapy (mean 1136+/-SE 105.7ng/ml, p=0.00001) and with therapy (mean 1073+/-52ng/ml, p=0.001) compared to controls (mean 819+/-28ng/ml). The highest levels were determined in sera of patients with a relapse (mean 1680+/-196ng/ml). By using immunofluorescence staining and confocal microscopy we determined immature dendritic cells as a major population of cystatin C positive cells in affected lymph nodes. Our study reports for the first time that cystatin C is a potential marker for relapse in patients with non-Hodgkin B-cell lymphoma.

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35. Pilav A, Nissinen A, Haukkala A, Niksic D, Laatikainen T. Cardiovascular risk factors in the Federation of Bosnia and Herzegovina. Eur J Public Health. 2007;17(1):75-9.

Department of Health statistics and informatics, Federal Public Health Institute Sarajevo, Bosnia and Herzegovina. idanap@bih.net.ba

BACKGROUND: Federation of Bosnia and Herzegovina (FBiH) has high cardiovascular disease mortality as other countries in Eastern Europe and situation has even deteriorated in the post war period. Reliable information on risk factor levels and patterns needed in prevention planning and disease management has been lacking. METHODS: A cross sectional population survey was conducted in the FBiH in autumn 2002. A random sample of population, aged 25-64 years, was taken using a three stage stratified sampling methodology. Altogether, 2750 persons participated in the survey (1121 men and 1629 women). The survey was done according to internationally established standards and protocols. RESULTS: The mean systolic blood pressure was 132 mmHg among men and 135 mmHg among women. The mean diastolic blood pressure was 84 mmHg in both genders. Almost 40% of the participants were recognized as hypertensive (blood pressure level over 140/90 mmHg). The prevalence of hypertension among men was 36% and among women 45%. The mean Body Mass Index (BMI) was 26.5 kg/m(2) among males and 27.0 kg/m(2) among females. About 75% of both men and women were overweight (BMI > 25 kg/m(2) and 16% of men and 20% of women were obese (BMI > 30 kg/m(2). About 50% of men and 30% of women reported to be daily smokers. CONCLUSIONS: As a whole the non-communicable disease risk factor levels in the FBiH seems to be relatively high. The data can be utilized in health promotion planning and as a baseline for future monitoring activities with possibility of international comparison of results.

Prepared by:
Husref Tahirović

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Sample References

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More than six authors:

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Organization as author:
Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40(5):679-86.

No author given:
21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

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Books and Other Monographs

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Dorland's illustrated medical dictionary. 29th ed. Philadelphia: W.B. Saunders; 2000. Filamin; p. 675.

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Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

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Foley KM, Gelband H, editors. Improving palliative care for cancer [monograph on the Internet]. Washington: National Academy Press; 2001 [cited 2002 Jul 9]. Available from: http://www.nap.edu/books/0309074029/html/.

Homepage/Web site:

Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/.

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American Medical Association [homepage on the Internet]. Chicago: The Association; c1995-2002 [updated 2001 Aug 23; cited 2002 Aug 12]. AMA Office of Group Practice Liaison; [about 2 screens]. Available from: http://www.ama-assn.org/ama/pub/category/1736.html

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